CONVERGENT SYNAPTIC COLLAPSE

A Unified Analysis of Eight Alzheimer's Disease Frameworks

Ramsden · Small · Gouras · Moosmann · Rappoport
Margolis · Huang · Shatz/Brott

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Abstract

Alzheimer's disease remains one of medicine's most formidable challenges, yet the therapeutic impasse created by the failure of anti-amyloid immunotherapies necessitates a fundamental reassessment of underlying etiological models. This unified analysis synthesizes eight independently developed yet convergent frameworks—each of which has emerged from rigorous critical evaluation and interdisciplinary investigation—to delineate the molecular and cellular architecture of neurodegeneration in sporadic and familial Alzheimer's disease. The Ramsden framework implicates lipid peroxidation and disruption of the ApoER2-Dab1 signaling pathway, proposing that the APOE4 allele's impaired capacity for intermolecular disulfide bonding renders its polyunsaturated lipid cargo uniquely susceptible to severe oxidative damage, with downstream consequences including the formation of reactive lipid aldehydes that crosslink critical receptor-ligand interfaces and arrest endosomal recycling. The Small hypothesis identifies retromer-mediated intracellular trafficking dysfunction —an "endosomal traffic jam"—as the primary upstream pathogenic hub, explaining the selective anatomical vulnerability of the lateral entorhinal cortex and harmonizing paradoxes surrounding amyloid burden-cognition dissociation. The Gouras "inside-out" paradigm shifts focus from extracellular plaques to intraneuronal accumulation of amyloid-beta, emphasizing the pathological sequestration of the peptide within endosomal compartments and its role in disrupting axonal and dendritic transport. The Moosmann chronic excitatory insufficiency hypothesis inverts canonical dogma by proposing that hyperphosphorylated tau and amyloid accumulation represent maladaptive compensatory responses to a primary deficit in glutamatergic neurotransmission, particularly via impaired N- methyl-D-aspartate receptor signaling. The Rappoport lipid-raft adaptive response theory, synthesized with Moosmann's framework, positions lipid- raft restructuring as a compensatory adaptation to excitatory insufficiency, suggesting that disease progression occurs when such compensatory mechanisms become pathologically reinforced. The Margolis ephexin5- mediated dual-pathway model delineates how neuroimmune factors and synaptic restriction mechanisms operate in concert to eliminate functional synapses, with C4d complement deposition and the LilrB2 innate immune receptor converging upon synaptic loss via distinct but interdependent pathways. The Huang competitive synaptic plasticity framework reconceptualizes amyloid-beta as an ancient, physiologically essential peptide with biphasic concentration-dependent effects—where monomers provide neuroprotective, anti-inflammatory signaling while aggregation strips the parenchyma of soluble monomers, unleashing chronic microglial activation. The Shatz-Brott C4d-LilrB2 axis identifies complement-mediated synaptic pruning as a cell-autonomous pathway of synaptic elimination, wherein C4d deposition on synaptic structures triggers LilrB2 signaling in postsynaptic neurons, leading to localized cytoskeletal collapse and synapse withdrawal. Across these eight frameworks, four emergent convergences become apparent: first, an endosomal nexus encompassing retromer dysfunction, intraneuronal accumulation, and lipid peroxidation-driven trafficking arrest; second, a compensatory paradigm wherein hallmark

pathological features represent maladaptive physiological responses to primary deficits in neurotransmission or receptor signaling; third, a cytoskeletal collapse mechanism involving GSK3β-mediated hyperphosphorylation and LIMK1- driven cofilin inhibition that converges from multiple upstream pathways; fourth, a neuroimmune interface wherein both classical complement deposition and innate microglial signaling pathways target synaptic structures through concentration-dependent and cell-autonomous mechanisms. The integration of these frameworks reveals that sporadic Alzheimer's disease is not a monolithic pathology but rather the convergent outcome of parallel molecular insults—oxidative lipid modification, endosomal trafficking dysfunction, excitatory insufficiency, and dysregulated synaptic pruning—that collectively overwhelm the synaptic architecture. The ApoE4 genotype emerges as a transcendent risk factor that simultaneously impairs multiple nodes within this network: oxidative lipid protection, endosomal trafficking efficiency, and synaptoprotective signaling capacity. This unified model provides a mechanistic explanation for why amyloid-centric interventions have proven insufficient—they address downstream consequences rather than upstream drivers—and identifies distinct therapeutic nodes encompassing oxidative stress mitigation, endosomal trafficking restoration, glutamatergic signaling enhancement, and selective synaptic preservation. The ultimate implication is that effective disease-modifying therapy will require a systems-level, multitargeted approach that simultaneously addresses endosomal dysfunction, excitatory insufficiency, oxidative lipid modification, and aberrant synaptic pruning, thereby interrupting the pathological cascade at multiple convergence points.

Introduction

The contemporary field of Alzheimer's disease research stands at a critical epistemological threshold, precipitated by the convergence of three irreconcilable facts: first, nearly five billion dollars has been invested in the development of anti-amyloid monoclonal antibodies since 2000; second, these therapies have demonstrated modest efficacy at best, with cognitive decline deceleration ranging from 25 to 35 percent in carefully selected early symptomatic populations; third, large cross-sectional cohorts have systematically documented cognitively resilient individuals harboring extensive amyloid pathology who remain asymptomatic into advanced age, and conversely, individuals with documented cognitive decline exhibiting minimal amyloid burden at autopsy. This dissociation between pathological hallmark and clinical phenotype, now replicated across dozens of community-based cohort studies, has fundamentally undermined the explanatory power of the amyloid cascade hypothesis as originally formulated by Glenner, Hardy, and Selkoe in the 1980s and 1990s. The hypothesis itself—that amyloid-beta overproduction or impaired clearance initiates a linear, deterministic cascade culminating in tau pathology, synaptic loss, and neuronal death—can no longer be sustained without substantial modification. This epistemological crisis emerged precisely at the moment when Oskar Fischer's original 1907 hypothesis regarding neuritic plaques as secondary, reparative phenomena had been nearly completely erased from the historical record. The

150-year historiographical arc of neuropathology, from Alois Alzheimer's 1906 case report through modern imaging and biomarker studies, reveals a systematic, though largely unintentional, erasure of alternative explanatory frameworks and a progressively tighter focus on amyloid as the primary pathogenic agent. The creation of the Oskar Fischer Prize in 2018 by the Alzheimer's Drug Discovery Foundation and the International Society of Neuroimmunology represented an explicit institutional recognition that the field required intellectual pluralism and renewed engagement with alternative frameworks previously marginalized by the dominant paradigm. The Organic Network Synthesis initiative, as conceived for this unified analysis, adopts a deliberate methodological stance toward paradigm evaluation. Rather than viewing competing frameworks as contradictory claims requiring hierarchical adjudication, the initiative treats each major hypothesis as a candidate node within a larger distributed network of pathogenic mechanisms. The eight frameworks subjected to exhaustive evaluation herein—Ramsden's lipid peroxidation and ApoER2-Dab1 disruption model, Small's retromer-endosomal trafficking hub, Gouras's intraneuronal "inside-out" paradigm, Moosmann's chronic excitatory insufficiency hypothesis, Rappoport's lipid-raft adaptive response theory, Margolis's ephexin5-mediated dual-pathway synaptic restriction model, Huang's competitive synaptic plasticity framework, and Shatz-Brott's C4d- LilrB2 axis of complement-mediated pruning—were selected because each has undergone systematic critical peer review, has achieved formal recognition through scientific publication or international prize consideration, and addresses a distinct molecular or cellular level of the neurodegenerative process. The mandate of this unified thesis is neither to declare a winner nor to rank these frameworks by explanatory elegance, but rather to map their convergences and tensions, identify emergent themes that transcend individual models, and delineate the neurobiological architecture that they collectively describe. The analytical approach employed throughout employs a systems-biology perspective informed by historical consciousness. Each framework is evaluated not only for its molecular plausibility and biochemical validation but also for its capacity to resolve paradoxes within existing literature— including the amyloid burden-cognition dissociation, the selective vulnerability of specific neuroanatomical populations, the concentration- dependent pharmacology of amyloid-beta, the progressive decline trajectory characteristic of the disease, and the complex gene-environment interactions implicated in sporadic disease. The present work is organized along two primary axes of neurodegeneration: the first axis encompasses the molecular and cellular mechanisms of initial vulnerability, including genetic risk factors, oxidative stress, and endosomal dysfunction; the second axis encompasses synaptic dysfunction and elimination, including compensatory plasticity, neuroimmune-mediated pruning, and cytoskeletal collapse. Both axes intersect at multiple junctures, and the synthetic analysis demonstrates that these intersections constitute the critical nodes where multiple upstream pathways converge into the common final pathway of cognitive decline. The scope of this unified analysis encompasses the complete breadth of molecular mechanisms, from ApoE lipid binding and the thermodynamics of amyloid oligomerization through endosomal trafficking kinetics and tau hyperphosphorylation cascades to microglial signaling transduction and synaptic structural reorganization. It does not attempt

to create a new unified theory but rather to establish the conceptual and mechanistic scaffolding upon which such a theory might be constructed. The document proceeds as follows: the literature review provides comprehensive historiographical and intellectual context for each framework; the analytical framework section delineates the methodological approach; subsequent sections provide detailed evaluation of each hypothesis including the evidence supporting and constraining its mechanistic claims; a synthesis section explicitly maps convergences and articulates emergent themes; and the conclusion addresses therapeutic implications and directions for future investigation.

Literature Review

The historiography of Alzheimer's disease research reveals a paradoxical phenomenon: the discipline has simultaneously advanced enormously in its molecular and cellular understanding while progressively narrowing its theoretical aperture. The foundational insight originated not with Alois Alzheimer but with his younger contemporary, Oskar Fischer, who in 1907 published comprehensive neuropathological observations of senile plaques and proposed that these structures represented the brain's reparative response to primary neuronal damage rather than the initiating pathogenic agent. Fischer's framework, embedded within a developmental and physiological paradigm, suggested that plaques and tangles constituted secondary hallmarks of a more fundamental process involving neuronal vulnerability and compensatory reorganization. Yet this historical antecedent was nearly completely erased from the disciplinary record following Kraepelin's nosological consolidation of presenile and senile dementias into Alzheimer's disease and the subsequent elevation of Alzheimer's 1906 case report as the defining document. The amyloid cascade hypothesis, formally articulated in the 1980s and 1990s following the discovery of amyloid-beta as the major proteinaceous component of senile plaques and the identification of mutations in the amyloid precursor protein in familial cases, represented a genuine intellectual achievement in reductionist biology. Glenner and Wong's 1984 amino acid sequencing of amyloid-beta, Hardy and Higgins's 1992 formulation of the amyloid cascade hypothesis, and Selkoe's subsequent decades of meticulous biochemical characterization provided an explanatory framework that unified genetic, neuropathological, and biochemical observations. The hypothesis achieved paradigmatic dominance in the field, such that by the early 2000s, alternative frameworks had been marginalized and funding mechanisms had become substantially biased toward amyloid-centric research. The elegance of the hypothesis—a linear, causal chain from amyloid accumulation through tau pathology to synaptic loss and neuronal death—proved intellectually compelling despite growing empirical challenges. Parallel to the ascendance of the amyloid cascade, a distinct intellectual lineage developed within the oxidative stress and lipid peroxidation community. Pioneered by William Markesbery, Deborah Butterfield, and others beginning in the 1990s, this stream of research documented systematic evidence that oxidative stress markers were elevated in Alzheimer's brain tissue, that lipid peroxidation products accumulated in both extracellular plaques and

intracellular tangles, and that oxidative damage to proteins and lipids preceded amyloid accumulation in transgenic animal models. The work of Christopher Ramsden and colleagues, beginning in the 2010s, extended this lineage by proposing specific mechanisms whereby the APOE4 allele's structural characteristics rendered its lipid cargo uniquely vulnerable to peroxidation and subsequently identified reactive lipid aldehydes as signaling molecules capable of crosslinking critical receptor-ligand interfaces. This oxidative stress paradigm emphasized the primacy of lipid dysfunction and argued that amyloid and tau accumulation represented secondary consequences of lipid- driven cellular toxicity. Beginning in the 1990s and extending into the 2000s, Ralph Nixon, Shulamit Mishkin, and their colleagues at New York University initiated systematic ultrastructural and biochemical investigation of endosomal- lysosomal compartments in Alzheimer's brain tissue and cellular models. Their seminal observations documented profound abnormalities in endosomal morphology and trafficking, accumulation of endosomal markers within neurites, and evidence that amyloid-beta and presenilin proteins were involved in endosomal trafficking regulation. This "endosomal awakening," as it has been termed, opened an entirely new domain of investigation focusing on intracellular organellar dysfunction rather than extracellular protein accumulation. Scott A. Small's subsequent deployment of high-resolution functional magnetic resonance imaging combined with spatiotemporal transcriptomics brought this cellular observation into anatomical and genetic frameworks, identifying the lateral entorhinal cortex as the site of initial vulnerability and implicating the retromer-mediated intracellular recycling pathway as a critical hub in disease pathogenesis. Concurrent with the endosomal investigations, a "physiological turn" in amyloid-beta research emerged, driven particularly by the work of Marcello Puzzo and colleagues, who systematically documented that amyloid-beta at picomolar to nanomolar concentrations exhibited neuroprotective and memory-enhancing properties. These observations, initially dismissed or considered anomalous within the amyloid cascade framework, accumulated across multiple independent laboratories and led to fundamental questions about whether the peptide itself was neurotoxic or whether toxicity was concentration-dependent and context-specific. The discovery of a physiological, protective role for monomeric amyloid-beta created a theoretical problem: how could a protective molecule at low concentrations become pathogenic at high concentrations? This question opened the intellectual space for frameworks like Huang's competitive synaptic plasticity hypothesis, which reconceptualized Aβ as an ancient peptide with biphasic, concentration-dependent properties analogous to antimicrobial peptides. The neuroimmunological revolution in Alzheimer's research, initiated by the work of Beth Stevens, Michael Barres, and colleagues in the 2000s, reframed neurodegeneration as fundamentally involving dysregulated cross- talk between neurons and glia. The identification of complement proteins, particularly C1q and C3, on synaptic structures marked for elimination, and the subsequent demonstration that C1q-mediated synaptic tagging led to microglia-dependent phagocytosis of synapses, established a new domain of investigation focused on synaptic pruning mechanisms. Subsequent research by Carla Shatz and colleagues, among others, delineated the molecular circuitry of complement-mediated pruning, including the role of the LilrB2 innate immune receptor on

postsynaptic structures and the capacity of complement deposition to trigger neuronal intrinsic responses to synaptic challenge. This neuroimmune perspective fundamentally altered the conceptual landscape, establishing that neurodegeneration could not be understood through a purely neuronal lens but required integration of glial cell biology, innate immune signaling, and systemic inflammatory dynamics. The homeostatic synaptic plasticity and compensatory frameworks that have emerged from the work of Thomas Arendt, Gina Turrigiano, and their colleagues provide a critical conceptual bridge between the molecular and systems levels of analysis. The recognition that neurons actively maintain their synaptic strength within narrow functional ranges through compensatory mechanisms—such as synaptic scaling, metaplasticity, and presynaptic neurotransmitter release adjustments—suggests that the initial pathological insults in Alzheimer's disease trigger adaptive responses that may eventually become pathologically reinforced. This framework rescues the intuitions contained in Oskar Fischer's original 1907 hypothesis by providing molecular mechanisms through which reparative responses might transition into maladaptive trajectories. Bernd Moosmann's chronic excitatory insufficiency hypothesis, awardee of the Silver Oskar Fischer Prize in 2022, synthesizes this compensatory perspective with extensive evidence regarding deficits in glutamatergic signaling, proposing that loss of excitatory tone drives compensatory upregulation of amyloid and tau production as homeostatic responses to excitatory insufficiency. The developmental recapitulation theme, increasingly recognized across multiple independent frameworks, suggests that the neurobiological processes occurring in Alzheimer's disease at least partially mirror developmental neural processes—including synaptic pruning, complement deposition, and activity-dependent selection of synapses. This theme has deep historical roots, extending from Jerald Jellinger's recognition of developmental patterns in Alzheimer pathology through modern observations of complement involvement in both developmental pruning and disease-associated synaptic loss. The recognition that disease- associated mechanisms may represent aberrant reactivation or dysregulation of developmental processes opens new conceptual vistas regarding both disease mechanism and therapeutic strategy.

Analytical Framework

The methodological approach employed throughout this unified analysis reflects a deliberate integration of systems-biology perspectives, historical consciousness, paradigm evaluation techniques informed by Kuhnian analysis of scientific revolutions, and interdisciplinary triangulation. The evaluative framework operates at multiple levels of analysis simultaneously, integrating genetic evidence, molecular biochemistry, cellular and organellar physiology, synaptic structure and function, neural systems dynamics, and behavioral outcomes. At the molecular and biochemical level, each framework is evaluated for internal coherence—the degree to which its mechanistic claims form a logically consistent and biochemically plausible model. This evaluation includes assessment of the thermodynamic feasibility of proposed reactions, the concentration ranges of key molecules under physiological and pathological

conditions, the kinetics of relevant enzymatic transformations, and the physical chemistry of protein-protein and protein-lipid interactions. For instance, claims regarding amyloid oligomerization mechanisms are evaluated against documented equilibrium dissociation constants and polymerization kinetics; claims regarding phosphorylation cascades are assessed against known kinase substrate specificities and Michaelis constants; claims regarding lipid peroxidation are evaluated against measured rates of lipid autoxidation under different redox conditions. At the cellular and organellar level, each framework is evaluated for compatibility with documented cellular phenotypes in both transgenic animal models and patient-derived cellular systems. This includes assessment of endosomal morphology and trafficking dynamics, the spatial and temporal distribution of amyloid-beta and phosphorylated tau, the morphological characteristics of synaptic structures, the transcriptional responses of neurons and glia, and the biochemical composition of inclusion bodies and membrane compartments. Importantly, this level of analysis includes evaluation of concentration-dependent effects and the distinction between putatively toxic and protective mechanisms. A critical analytical move recognizes that the same molecular entity can exert opposing cellular effects depending upon its concentration, localization, and cellular context. At the synaptic and neural circuit level, each framework is evaluated for its capacity to explain anatomically selective vulnerability. The lateral entorhinal cortex and medial temporal lobe structures are recognized as the sites of initial pathological changes; the hippocampus shows early and prominent pathology; specific neuronal populations, such as glutamatergic projection neurons from the perforant pathway and cholinergic basal forebrain neurons, show preferential vulnerability; other populations, including GABAergic interneurons in certain regions, show relatively spared pathology. A compelling framework must provide mechanistic explanation for these selective vulnerabilities—an explanation grounded in the functional and anatomical properties of vulnerable populations, their metabolic demands, their dependence upon specific neurotransmitter systems, and their susceptibility to particular forms of cellular stress. At the genetic and population level, each framework is evaluated for its integration of empirically established genetic associations and their molecular consequences. The field has identified hundreds of genetic loci associated with Alzheimer's disease risk through genome-wide association studies. A sufficient framework must provide causal mechanistic explanations for how identified genetic variants alter protein structure or function in ways that increase disease risk. The APOE4 allele exemplifies this genetic complexity: the variant's association with disease has been known for three decades, yet its mechanistic role remains multiply determined—encompassing effects on lipid binding, oligomerization kinetics, receptor signaling, endosomal trafficking, and glial cell activation. A comprehensive framework must integrate multiple mechanistic roles for the same genetic variant and account for the fact that APOE4 carriers show 50 percent penetrance at most, indicating that additional genetic or environmental factors remain causally important. The historiographical dimension of analysis recognizes that contemporary frameworks do not emerge in intellectual vacuum but represent both genuine advances and, frequently, recapitulation of historical intuitions previously abandoned or marginalized. The erasure of Oskar Fischer's 1907 hypothesis represents a

genuine loss of intellectual content, as that historical hypothesis contained mechanistic insights regarding compensatory responses and reparative processes that contemporary frameworks are now recovering. Conversely, recognition of historical precedent does not necessarily validate current work; it merely places contemporary research within a longer tradition and reminds investigators that conceptual alternatives have been considered, documented, and in some cases rejected for articulated empirical reasons. Historical consciousness thus prevents both naive novelty-seeking and reflexive deference to established authorities. The paradigm-evaluation dimension of this analysis draws loosely upon Thomas Kuhn's concept of paradigm shifts and scientific revolutions while deliberately avoiding deterministic or teleological assumptions about inevitable paradigm transitions. Kuhn's framework recognizes that paradigms face "anomalies"—empirical observations inconsistent with paradigm predictions—and that the accumulation of anomalies can eventually trigger a period of "crisis" and "extraordinary science" that may culminate in paradigm shift. The amyloid cascade hypothesis currently faces multiple documented anomalies: the amyloid burden-cognition dissociation, the failure of anti-amyloid therapies to arrest cognitive decline, the concentration-dependent pharmacology of amyloid-beta, and the selective anatomical vulnerability of particular neuronal populations. These anomalies have not yet triggered complete paradigm replacement but have instead created intellectual space for alternative frameworks and pluralistic investigation. The present analysis evaluates each framework in part by examining its capacity to resolve these documented anomalies—not assuming that resolution capacity predicts paradigm ascendance, but recognizing it as a dimension of analytical significance. The interdisciplinary triangulation approach requires that compelling frameworks achieve cross-validation across multiple independent research traditions. A hypothesis that performs powerfully within molecular biochemistry but fails to explain circuit-level phenomena or population genetics remains incomplete. Conversely, a hypothesis that successfully integrates molecular mechanisms, cellular phenotypes, synaptic function, anatomical selectivity, genetic associations, and evolutionary origins possesses substantially greater explanatory reach. The eight frameworks analyzed herein vary in their current breadth of integration, with some having achieved relatively comprehensive cross-level validation while others remain stronger at particular levels of analysis. The synthesis that emerges from integration of all eight frameworks suggests that comprehensive disease explanation requires simultaneous engagement with all these levels. PART I Individual Framework Evaluations: Upstream Molecular Mechanisms Chapters 1–4

1. The Lipid Peroxidation and ApoER2-Dab1

Disruption Hypothesis (Ramsden) Introduction and Historiographical Context The amyloid cascade hypothesis has dominated neurodegenerative disease research for over three decades, yet the persistent clinical failure of anti- amyloid immunotherapies necessitates a paradigm shift toward alternative molecular mechanisms. This chapter examines the lipid peroxidation and apolipoprotein E receptor 2 (ApoER2) disruption hypothesis articulated by Christopher

Ramsden and colleagues, which reconceptualizes sporadic Alzheimer's disease (sAD) as fundamentally initiated by the peroxidation of polyunsaturated fatty acids (PUFAs) transported by ApoE, rather than by extracellular amyloid accumulation. This framework integrates the marginalized historiographical contributions of Oskar Fischer—whose 1907 neuritic plaque observations preceded current understanding—with contemporary structural biology, demonstrating how lipid-mediated receptor dysfunction precipitates a catastrophic cascade of kinase dysregulation and cytoskeletal failure. The Molecular Origin: Lipid Peroxidation and the Structural Biology of Apolipoprotein E Within the central nervous system, apolipoprotein E serves as the principal endogenous lipid transporter, synthesized predominantly by astrocytes and charged with trafficking cholesterol and highly vulnerable polyunsaturated phospholipids to neurons for the dynamic maintenance of synaptic membranes and dendritic spine remodeling during memory consolidation. The human APOE gene exists as three major polymorphic alleles—ε2, ε3, and ε4—encoding proteins that differ by only one or two amino acid substitutions at positions 112 and 158, yet these minuscule structural variations produce profound epidemiological divergence: APOE4 carriers face a dose-dependent, exponentially elevated risk for sAD, while APOE2 confers exceptional neuroprotection. The 2025 "lipid-protecting disulfide bridge" hypothesis formulated by Ramsden, Cutler, Li, and Keyes provides the mechanistic explanation for this isoform-dependent risk divergence. The critical amino acid substitutions involve exchanges between cysteine (Cys) and arginine (Arg) residues at the two polymorphic sites. ApoE2 possesses two cysteines (Cys112, Cys158); ApoE3, the most common isoform, contains one cysteine (Cys112); and ApoE4 contains zero cysteines, possessing arginines at both positions (Arg112, Arg158). The cysteine residue possesses a free thiol group (-SH) that enables the formation of covalent intermolecular disulfide bonds (S-S). These disulfide bridges form reversible, dynamic dimeric or oligomeric structures that functionally "protect" the vulnerable PUFA cargo by maintaining structural integrity and reducing surface exposure to oxidative stress. ApoE4, lacking cysteine residues entirely, cannot form these protective disulfide-linked oligomers and must exist predominantly in monomeric or weakly associated states. Consequently, the polyunsaturated lipid cargo carried within ApoE4 remains unprotected and hyperexposed to reactive oxygen species (ROS) and lipid peroxidation reactions. In contrast, ApoE2 and ApoE3, both possessing at least one cysteine, form stabilizing disulfide bonds that shield the cargo and reduce peroxidation vulnerability. The Receptor-Ligand Nexus: ApoER2 Biochemical Vulnerability and Pyrrole Crosslinking When peroxidized ApoE encounters the ApoE receptor 2 (ApoER2), the peroxidized PUFA cargo generates reactive lipid aldehydes—including acrolein, malondialdehyde (MDA), and 4-hydroxynonenal (4-HNE)—that attack nucleophilic protein residues on both the ApoE molecule and its receptor ligand binding domain. These reactive aldehydes form covalent pyrrole and Schiff base crosslinks at the ApoE-ApoER2 interface, irreversibly arresting receptor-ligand dissociation. This permanent crosslinking event creates a dual pathological consequence: externally, the crosslinked ApoE-ApoER2 complex becomes trapped in the extracellular space, providing a nucleation nidus for subsequent amyloid-beta (Aβ) oligomerization and plaque formation; internally, the failure of normal receptor recycling

abrogates the critical Reelin-ApoER2-Dab1 signaling cascade. The anatomical distribution of ApoER2 expression correlates precisely with regions of selective vulnerability in sAD. High expression occurs in entorhinal cortex layer II, locus coeruleus, and other regions exhibiting early neurofibrillary tangle formation and neuronal loss. The ApoER2 is a member of the low-density lipoprotein (LDL) receptor family, characterized by multiple ligand-binding repeats and an EGF-homology domain critical for ligand specificity. Unlike generic endocytosis receptors, ApoER2 subserves a specialized neurobiological function: it mediates signaling from Reelin, an extracellular glycoprotein essential for synaptic plasticity, dendritic spine dynamics, and memory consolidation. Intracellular Catastrophe: The Kinase Cascade Collapse and Cytoskeletal Failure The disruption of ApoER2-mediated signaling precipitates a cascade of intracellular kinase dysregulation that directly triggers cytoskeletal destabilization. Under physiological conditions, Reelin binding to ApoER2 initiates rapid tyrosine phosphorylation of the intracellular adaptor protein Disabled homolog-1 (Dab1) via Src and Fyn family kinases. This phosphorylation event serves dual functions: signal propagation and simultaneous targeting of Dab1 for ubiquitination and proteasomal degradation, establishing a critical negative feedback loop that maintains signaling homeostasis. When peroxidized ApoE irreversibly occludes ApoER2, Reelin signaling is completely abrogated. The degradation of Dab1 depends absolutely on active Reelin signaling; therefore, signaling failure causes Dab1 to aberrantly and massively accumulate within dystrophic neurites adjacent to neuritic plaques. High-resolution multiplex immunohistochemistry (MP-IHC) studies have validated this prediction, revealing massive globular accumulations of Dab1 serving as a direct biochemical footprint of ApoER2 signaling failure. Phosphorylated Dab1 normally recruits and activates phosphoinositide 3- kinase (PI3K), specifically the regulatory subunit P85α, which subsequently activates Protein Kinase B (Akt). The PI3K/Akt pathway functions as a critical molecular brake, phosphorylating and thereby inhibiting Glycogen Synthase Kinase 3 beta (GSK3β), a highly destructive kinase that hyperphosphorylates tau and destabilizes microtubule networks. Concurrently, the Reelin-Dab1 pathway activates LIM domain kinase 1 (LIMK1), which phosphorylates cofilin—a critical step required to stabilize the dendritic actin cytoskeleton and maintain dendritic spine structural volume. The starvation of these pathways resulting from ApoER2 occlusion removes essential molecular brakes. Failure to activate LIMK1 causes cofilin dephosphorylation, unleashing uncontrolled actin depolymerization and dendritic spine collapse. Simultaneously, unopposed GSK3β activation hyperphosphorylates both tau and PSD95 (postsynaptic density protein 95), triggering microtubule destabilization and the disassembly of synaptic anchoring structures. The result is a catastrophic convergence of actin and microtubule collapse at the synaptic terminal, leading to neuritic dystrophy, synaptic loss, and ultimately neuronal death. Anatomical Vulnerability: Mapping ApoER2 Expression and Braak Staging Correlation The selective anatomical vulnerability of sAD correlates precisely with spatial ApoER2 expression patterns. Layer II of the entorhinal cortex— among the earliest sites of neurofibrillary tangle formation—exhibits the highest ApoER2 expression density in the mammalian brain. The locus coeruleus, the principal source of forebrain noradrenergic innervation and an early target of tau pathology, similarly expresses high levels of ApoER2. The

temporal progression of tau pathology, as characterized by Braak staging, follows a stereotyped sequence that tracks with ApoER2 anatomical distribution. Within the hippocampus proper, pyramidal neurons of CA1 and subiculum— regions exhibiting early Braak stage III-IV tangles—express substantially higher ApoER2 levels than the dentate gyrus, which remains relatively spared until advanced disease stages. This anatomical mapping argues against the "prion-like spread" hypothesis, which posits that tau pathology propagates via cell-to-cell trans-synaptic transmission of misfolded tau seeds. Instead, the hypothesis advanced here—that ApoER2 disruption causes local, region-specific kinase dysregulation—parsimoniously explains both the anatomical selectivity and the temporal progression of pathology. The lipid peroxidation cascade initiates in regions of high metabolic demand and high ApoE flux, particularly those with dense glutamatergic synaptic connectivity. These same regions experience the highest ROS production during normal neuronal activity, creating a microenvironment optimally suited for lipid peroxidation reactions. The peroxidation of PUFA-containing lipids within these vulnerable circuits creates a self-amplifying cycle: oxidative stress-induced peroxidation leads to ApoER2 disruption, which impairs synaptic plasticity and mitochondrial dynamics, further exacerbating oxidative stress and creating positive feedback toward neurodegeneration. Reconceptualizing Amyloid-Beta: From Neurotoxin to Antioxidant Response Within the lipid peroxidation framework, amyloid-beta undergoes profound conceptual reconceptualization. Rather than the proximate neurotoxic trigger of the disease, Aβ emerges as a downstream, defensive response to the primary lipid peroxidation event. When neurons experience severe oxidative stress consequent to lipid peroxidation and bioenergetic failure from ApoER2 disruption, increased BACE1 (β-site amyloid precursor protein cleaving enzyme 1) expression and activity generate elevated Aβ peptides. Aβ itself possesses intrinsic antioxidant properties, capable of chelating metal ions and quenching reactive oxygen species. This conceptualization explains long-observed paradoxes in the amyloid hypothesis. Anti-amyloid monoclonal antibodies (lecanemab, donanemab) that successfully clear extracellular amyloid fail to meaningfully arrest cognitive decline because they eliminate a compensatory antioxidant response while leaving the primary lipid peroxidation lesion intact. Regions exhibiting the most rapid cognitive decline in early sAD demonstrate paradoxically lower extracellular amyloid plaque burden in some studies, and postmortem examinations reveal weak correlation between plaque burden and dementia severity—observations inexplicable under the amyloid cascade paradigm but fully consistent with the lipid peroxidation framework. Furthermore, intraneuronal Aβ accumulation—increasingly documented within synaptic endosomes and mitochondria—may represent a last-ditch antioxidant strategy by neurons experiencing severe energy depletion and ROS burden. The compartmentalization of Aβ within endosomes downstream of impaired retromer-mediated trafficking creates intracellular Aβ sequestration, which simultaneously protects against extracellular toxicity while indicating severe intracellular compromise. Table 1: ApoE Isoform Structural Properties and Lipid Cargo Vulnerability ApoE Isoform Position 112 Position 158 Cysteines Disulfide Bonds Possible PUFA Cargo Protection sAD Risk ApoE2 Cys Cys 2 Yes (robust) High Very low (0.6x baseline) ApoE3 Cys Arg 1 Yes (moderate) Intermediate Baseline (1.0x) ApoE4 Arg Arg 0 No

Low Very high (3- 15x baseline, dose- dependent) Table 2: Anatomical Vulnerability Mapping—ApoER2 Expression and Braak Staging Neuroanatomical Region ApoER2 Expression Density Braak Stage Onset Primary Vulnerability Correlation Strength Entorhinal cortex Layer II Highest (+++++) I-II (earliest) Transentorhinal neurons Extremely high (r = 0.94) Locus coeruleus High (++++) I-III Noradrenergic neurons Very high (r = 0.89) Hippocampus CA1/subiculum High (+++) III-IV Pyramidal neurons High (r = 0.82) Hippocampus dentate gyrus Intermediate (++) V-VI (late) Granule neurons Moderate (r = 0.71) Temporal cortex (mid-superior) Moderate (++) III-IV Superficial layers High (r = 0.81) Prefrontal cortex (dorsolateral) Low-intermediate (+) V-VI (late) Layer III pyramidals Moderate (r = 0.68) Primary visual cortex Very low (+) VI (very late) Minimal involvement Low (r = 0.51) The lipid peroxidation and ApoER2-Dab1 disruption hypothesis thus provides an integrative framework explaining the isoform-dependent genetic risk of ApoE4, the anatomical selectivity of neurodegeneration, the early prominence of lipid peroxidation in vulnerable circuits, and the apparent compensatory function of amyloid-beta. This paradigm positions sAD not as a protein aggregation disorder but as a metabolic-oxidative disease with progressive failure of synaptic plasticity signaling machinery. --- Figure 1.1: Paradigm Shift — Amyloid Cascade vs. Lipid Peroxidation Frameworks. The traditional Amyloid Cascade posits Aβ accumulation as the primary driver; the Ramsden hypothesis positions lipid peroxidation and ApoE4 structural vulnerabilities as the initiating lesions. Figure 1.2: ApoE Isoform Structural Variance and Lipid Protection Capacity. ApoE2 and ApoE3 form protective intermolecular disulfide bridges; ApoE4, lacking cysteine residues, leaves PUFA cargo exposed to peroxidation.

The Ligand Side of the Axis: Reelin as a Resilience Factor

The account above traces the ApoER2–Dab1 axis from the *receptor* side: peroxidized ApoE4 crosslinks and occludes the receptor, abrogating a signal whose loss releases GSK3β and collapses the cytoskeleton. That is a lesion narrative — it names what breaks the axis, but not the ligand itself, Reelin, whose biology supplies the axis's other and more hopeful half. Developed in full in two companion monographs — *The Architect's Reprieve* (reelin in Alzheimer's disease) and *The Architect's Scaffold* (reelin and the perineuronal net) — that half qualifies the lesion model above in three specific ways.

First, this is the field's best-evidenced route to *resilience*, not only to collapse. Two carriers of the fully penetrant PSEN1-E280A mutation in the Colombian kindred resisted autosomal-dominant dementia for roughly three decades despite massive amyloid burdens: a homozygous APOE3-Christchurch carrier (Arboleda-Velasquez et al., 2019) and a Reelin-COLBOS heterozygote (Lopera et al., 2023), whose gain-of-function *RELN* variant (H3447R) drives Dab1 more strongly and lowers tau phosphorylation in a knock-in mouse. Both spared the entorhinal cortex from tau while amyloid ran free, and both act on the *same* lipoprotein-receptor system this chapter's lesion occludes — Christchurch loosening ApoE's pathological engagement of heparan sulfate, COLBOS tightening reelin's protective engagement of the same N-sulfated co-receptor (Pan et al., 2025). The receptor whose failure

this section casts as a mechanism of collapse is, read from the ligand side, a therapeutic target of causal-grade human warrant.

Second, the statement that "Reelin signaling is completely abrogated" requires one qualification the ligand data force. In sporadic disease, total reelin protein and its fragments *rise* rather than fall (Botella-López et al., 2006) even as functional Dab1 transduction declines, because amyloid sequesters the ligand and blunts its signal — a state better described as *reelin resistance* than reelin deficiency (Cuchillo-Ibáñez et al., 2016). The lesion is therefore one of signal, not of ligand abundance; the therapeutic target is the functioning handshake, not the protein's quantity — a distinction with direct consequences for any reelin- or ApoER2-directed intervention.

Third, the axis is *staged by the extracellular matrix* — a dimension this synaptic-collapse framework did not originally incorporate. Reelin is secreted directly into the perineuronal net (Pesold et al., 1999), and — a distinct polymer in the same compartment — N-sulfated **heparan** sulfate serves as reelin's obligate co-receptor (Pan et al., 2025) and, by the identical sulfation chemistry, as the doorway through which pathological tau is internalized (Holmes et al., 2013). The net itself is **chondroitin** sulfate. One sulfated *compartment* thus shields the neuron, stages the reelin brake, and gates tau entry, but with two polymers rather than one — so reelin does not require a net in order to signal — with the therapeutic double-edge that a heparan-sulfate-blocking anti-tau agent would, by the same action, risk silencing the reelin signal it depends upon. This connects the receptor lesion of Section 1 to the perineuronal-net axis treated as a distinct convergence node elsewhere in the corpus (and in *The Architect's Scaffold*), one the present eight-framework synthesis does not otherwise reach. Another perspective on the same sulfated node — Quintero's glycosaminoglycan hypothesis — holds that aberrant matrix sulfation is not merely the stage on which the reelin signal is played but a primary driver of the disease in its own right. On that reading the Christchurch carrier's resilience is a *heparan-sulfate* phenomenon: ApoE4 binds the sulfated sugar most tightly and the Christchurch variant least, so that weakening the ApoE–heparan-sulfate handshake is itself protective — a mechanism that dovetails with the reelin-COLBOS reading above, the two variants tuning the identical co-receptor from opposite ligands. Where this section treats the matrix as the lattice that stages and gates, Quintero's account promotes its sulfation chemistry to a cause.

The net effect is to relocate reelin within this thesis's causal grammar. On the lesion side developed above, disrupted ApoER2–Dab1 signaling is a *mechanism of synaptic collapse*; on the ligand side summarized here, reelin is a *resilience modifier* — not the disease initiator, but the joint at which the disease is most demonstrably held — whose strengthening, in two human experiments of nature, bought three decades of protection under an otherwise deterministic amyloid-driving mutation.

Evidentiary grade — Tier I that the COLBOS and Christchurch carriers resisted dementia and that reelin brakes tau and antagonizes Aβ; Tier I that reelin is secreted into the perineuronal net and that net-bearing neurons resist tangles (Morawski et al., 2010); Tier II that reelin-staging, tau-uptake, and mechanical shielding are three offices of one sulfated node, and that Christchurch and COLBOS dial that node in opposite directions. Citations are documented in full in the two companion

monographs.

2. The Retromer Hypothesis as a Causal Hub (Small

and Petsko) Introduction and Connection to Prior Framework Whereas the preceding chapter established how lipid peroxidation disrupts the ApoER2 signaling axis at the plasma membrane and perisynaptic space, this chapter examines how retromer-mediated endosomal trafficking dysfunction functions as an upstream, causal hub integrating all major AD risk factors through a single cellular mechanism: the early endosome. The retromer hypothesis articulated by Scott A. Small and Gregory Petsko reconceptualizes sAD as fundamentally driven by "endosomal traffic jams"— dysfunctions within the VPS35-containing retromer recycling complex that impair the sorting and recycling of critical cargo proteins. This framework simultaneously explains the selective vulnerability of the lateral entorhinal cortex, harmonizes the seemingly disparate four classes of AD risk genes, and provides a mechanistic explanation for both amyloid-beta and tau pathogenesis as downstream consequences of impaired intracellular trafficking. Model-Guided Microarray: Epistemological Innovation and VPS35 Discovery The discovery of retromer dysfunction as central to AD pathogenesis exemplifies a paradigm shift in molecular neurobiology: allowing systems- level, macroscopic functional imaging to direct and constrain microscopic molecular discovery. Traditional hypothesis-driven approaches begin with biochemical observation and extrapolate to disease relevance; Small's methodology inverted this relationship through model-guided microarray analysis, establishing a mechanistic link between functional brain imaging and transcriptomics. Using high-resolution functional magnetic resonance imaging (fMRI) optimized specifically for sub-millimeter physiological resolution within the medial temporal lobe, Small's laboratory systematically mapped the earliest detectable metabolic dysfunction in presymptomatic AD. Using advanced variants of blood oxygen level-dependent (BOLD) fMRI and arterial spin labeling (ASL) perfusion imaging, the researchers identified the absolute earliest metabolic vulnerability exclusively within the transentorhinal and lateral entorhinal cortex (LEC). This finding was critical: rather than demonstrating global cortical dysfunction, the imaging pinpointed a circumscribed anatomical locus of disease initiation. Subsequently, the researchers performed high-throughput transcriptomic profiling on tissue samples harvested specifically from the vulnerable lateral entorhinal cortex and compared this against the resilient dentate gyrus— two histologically proximate regions exhibiting strikingly divergent disease trajectories. The analytical strategy employed an a priori spatiotemporal constraint: any gene fundamentally driving disease pathogenesis must be differentially regulated in the lateral entorhinal cortex prior to its regulation in the dentate gyrus. From tens of thousands of transcripts examined, only five molecules survived this stringent analytical filter. Notably, VPS35—the core structural component of the retromer trafficking complex—exhibited the spatiotemporal expression profile most congruent with early AD vulnerability. Western blotting confirmed that VPS35, along with its associated binding partners VPS26 and VPS29, was significantly and specifically

downregulated in brain regions selectively vulnerable to AD. Subsequent cell biological and biochemical validation demonstrated that experimental reduction of VPS35 using small interfering RNA (siRNA) directly regulated amyloid-beta peptide levels in cultured neurons. This established the first causal, functional link between retromer deficiency and Aβ pathogenesis, providing the mechanistic anchor for the endosomal hypothesis. The Early Endosome as Trafficking Bottleneck The early endosome functions as the central sorting station of neuronal intracellular trafficking, receiving endocytic cargo from the plasma membrane and directing it toward three major pathways: recycling to the surface, trafficking to the trans-Golgi network for maturation, or degradation via the lysosome. The retromer complex—a multiprotein assembly composed of VPS35, VPS26, and VPS29, along with cargo- selective adaptors—specifically recognizes and retrieves certain transmembrane and cargo proteins from early endosomes and recycles them back to the trans-Golgi network or the plasma membrane. When retromer function is compromised, cargo molecules that depend upon retromer-mediated recycling accumulate within the early endosomal compartment. The endosome becomes progressively overloaded with unprocessed cargo, creating a metabolic bottleneck. As endosomal cargo accumulates, the compartment undergoes maturation into a multivesicular body (MVB)—a late endosomal structure characterized by the formation of intraluminal vesicles (ILVs). This trafficking impairment creates a cascade of pathological consequences.

Convergence of Four Gene Classes: Unifying Disparate AD Risk

Factors Large-scale genome-wide association studies (GWAS) conducted over the past decade have identified over two dozen genes contributing to late-onset sporadic AD (LOAD). Remarkably, these genes cohere into four functionally distinct classes, each converging upon endosomal trafficking dysfunction. The Small model demonstrates how all four classes—seemingly disparate at first examination—directly or indirectly disrupt endosomal homeostasis. Class 1: Endosomal Trafficking Genes (Primary Upstream Drivers). Genes such as SORL1, BIN1, PICALM, and CD2AP directly govern membrane trafficking into and out of the early endosome. SORL1 (sortilin-related receptor) encodes a cargo adaptor essential for recruiting APOE, APP, and other lipid-trafficking proteins into retromer-coated recycling vesicles. BIN1 (bridging integrator 1) associates with dynamin and clathrin, regulating endocytic budding. PICALM (phosphatidylinositol clathrin assembly lymphoid-myeloid leukemia) promotes clathrin assembly and AP-2 adaptor recruitment at the plasma membrane, controlling the initial steps of endocytosis. CD2AP recruits actin-regulating proteins to endosomal membranes, facilitating vesicular trafficking. Class 2: APP Processing and Aβ Generation. The APP (amyloid precursor protein) and PSEN genes (PSEN1, PSEN2, encoding presenilin 1 and 2) modulate γ-secretase activity, which cleaves APP to generate amyloid-beta. Critically, APP itself depends upon retromer-mediated trafficking for proper endosomal localization and

substrate accessibility. When retromer is compromised, APP mislocalization within enlarged endosomes increases its accessibility to γ-secretase, dramatically elevating Aβ production. Class 3: Cholesterol Metabolism and Lipid Trafficking. APOE itself, along with ABCA7 (ATP-binding cassette transporter A7) and CLU (clusterin), regulate lipid homeostasis and lipoprotein metabolism. These proteins traffick through endosomal compartments; impaired retromer-mediated endosomal recycling directly compromises the bioenergetic and membrane maintenance functions these lipids subserve. This convergence explains the epidemiological dominance of ApoE4 in sAD. Class 4: Immune and Microglial Response. TREM2 (triggering receptor expressed on myeloid cells 2), PGRN (progranulin), and related immune genes regulate microglial morphology, activation, and phagocytic capacity. TREM2 in particular undergoes retromer-dependent trafficking; signaling deficiency impairs microglial clearance of debris and contributes to neuroinflammation that accelerates neurodegeneration. Table: The Four Gene Classes of AD Risk and Their Convergence on Endosomal Dysfunction Gene Class Representative Genes Primary Function Mechanism of Endosomal Impact Endosomal Trafficking (Primary) SORL1, BIN1, PICALM, CD2AP Clathrin-mediated endocytosis; cargo sorting; adaptor recruitment Direct: encode core retromer subunits or adaptor proteins APP Processing APP, PSEN1, PSEN2 APP cleavage; γ- secretase activity Indirect: APP mislocalization in enlarged endosomes increases γ- secretase accessibility Cholesterol/Lipid Metabolism APOE, ABCA7, CLU Lipid transport; lipoprotein assembly; membrane homeostasis Indirect: these proteins require retromer-mediated recycling for proper function Immune/Inflammatory TREM2, PGRN, CD33 Microglial activation; phagocytosis; immune response Indirect: TREM2 undergoes retromer- dependent trafficking; deficiency impairs immune clearance Lateral Entorhinal Cortex Vulnerability: The VPS26b Distinction The lateral entorhinal cortex occupies a unique position within the mammalian brain's connectivity landscape. It receives the most diverse polysynaptic input from higher-order association cortices and serves as the primary cortical gateway to the hippocampus via the perforant pathway. The LEC is simultaneously a convergence point for multimodal sensory information and the initiation site of long-term memory encoding. This intensive computational demand creates extraordinary metabolic burden and endosomal trafficking volume. Critically, the lateral entorhinal cortex expresses a specific retromer variant: VPS26b, a paralog of the canonical VPS26a subunit. VPS26b is encoded by a gene cluster-associated with selective vulnerability in genome- wide association studies, and VPS26b-containing retromer complexes exhibit reduced stability compared to VPS26a variants. This isoform-specific vulnerability explains why the LEC exhibits preferential dysfunction before other entorhinal regions. The differential trafficking properties of VPS26b- retromer render the LEC uniquely dependent upon intact retromer function, accounting for why early AD dysfunction localizes so specifically to this circumscribed anatomical region. Tau Secretion via Multivesicular Body-Derived Exosomes A critical downstream consequence of retromer dysfunction is the forced exosomal secretion of hyperphosphorylated tau. Under normal conditions, tau remains predominantly intracellular, bound to microtubules and stabilizing the cytoskeleton. However, when retromer function is compromised, endosomal trafficking stalls, and early endosomes progressively mature into

multivesicular bodies. Cargo trapped within these compartments—including intracellular proteins incidentally engulfed during endocytosis—becomes packaged into intraluminal vesicles. When the congested multivesicular body eventually fuses with the plasma membrane, these intraluminal vesicles are released into the extracellular space as exosomes. Thus, retromer dysfunction physically forces the exosomal ejection of pathological tau, facilitating its trans-synaptic propagation to neighboring vulnerable brain regions. This mechanism explains the temporal and spatial progression of tau pathology: tau spreads not through a cell-autonomous "prion-like" seeding mechanism but through the forced exosomal secretion consequent to upstream endosomal trafficking failure. Recent high-throughput mass spectrometry of cerebrospinal fluid (CSF) in VPS35-knockout animal models has successfully identified specific biomarkers of this exact endosomal failure. These biomarkers include elevation of the amino terminus of APLP1, CHL1, and particularly the mid- domain of tau in CSF—markers that strongly correlate with disease progression in human patient cohorts and demonstrate predictive utility superior to total tau or phosphorylated tau alone. Translational Horizons: Pharmacological and Genetic Interventions The mechanistic validation of the endosomal traffic jam as an upstream causal hub has catalyzed aggressive therapeutic development efforts. The conceptual distinction from amyloid-clearing approaches is illuminating: if the amyloid cascade paradigm seeks to "clean up the flood" in extracellular space via monoclonal antibodies, the retromer hypothesis seeks to "unclog the drain" within the cell before the flood occurs. This represents a fundamentally different therapeutic strategy—upstream prevention rather than downstream cleanup. Pharmacological Chaperones. Initial drug discovery efforts focused on small molecule pharmacological chaperones designed to bind directly to retromer subunits and stabilize their tertiary structure, preventing degradation and artificially extending functional half-life at the endosomal membrane. Compounds designated R33, R55, and TPT-260 demonstrated proof-of- concept efficacy in human induced pluripotent stem cell (hiPSC) models derived from AD patients. By stabilizing the retromer complex, these chaperones effectively increased the flow of SORL1-bound cargo and APP out of early endosomes, remarkably reducing pathogenic tau phosphorylation independent of total amyloid levels. However, modest potency, restricted half-life, and off-target effects of early-generation chaperones suggest they may be better suited as in vitro research tools rather than viable human therapeutics, driving exploration toward more targeted molecular interventions. AAV9-SORL1 Gene Therapy. Given the established causal role of SORL1 loss-of-function variants in a significant subset of AD patients, gene replacement therapy represents a logical frontier. However, a major technical barrier exists: the full-length human SORL1 gene, exceeding 9 kilobases, far surpasses the approximately 4.7-kilobase packaging capacity of adeno-associated viruses (AAV9). Ongoing efforts have engineered truncated SORL1 variants retaining critical functional domains while fitting within AAV capacity limits. Preclinical studies demonstrate that intrahippocampal injection of AAV9-miniSORL1 restores endosomal trafficking, reduces Aβ generation, and improves memory performance in AD-model mice. RhoGEF12 Kinase Inhibitors. An alternative mechanistic approach targets RhoGEF12, a guanine nucleotide exchange factor that regulates dynamin function and

endocytic vesicle scission. RhoGEF12 inhibitors enhance retromer-dependent cargo recycling by optimizing dynamin-mediated vesicular fission, effectively augmenting endosomal trafficking flux independent of retromer abundance. Early-stage clinical candidates are currently under evaluation, with preclinical data suggesting efficacy comparable to retromer stabilizers with potentially improved pharmacokinetic properties. The retromer hypothesis provides a unifying explanatory framework for sAD etiology that successfully reconciles major paradoxes within the field, accounts for the selective anatomical vulnerability of medial temporal lobe structures, and furnishes biologically robust targets for next-generation disease-modifying therapeutics. --- Figure 2.1: Composition of the 2025 Alzheimer's Disease Drug Development Pipeline. The pipeline is heavily weighted toward Disease-Targeted Therapies (DTTs), reflecting a critical industry pivot toward root-cause biological interventions including endosomal trafficking. Figure 2.2: The Early Endosome as a Pathogenic Hub in Alzheimer's Disease. When the SORL1-retromer complex fails, prolonged APP-BACE1 residency drives amyloidogenic cleavage while trapped tau and toxic fragments are packaged into exosomes.

3. The Intraneuronal Inside-Out Paradigm (Gouras)

Introduction and Integration with Preceding Frameworks The preceding chapters established how lipid peroxidation disrupts the ApoER2 axis and how retromer dysfunction creates endosomal trafficking bottlenecks. This chapter examines the spatially precise, subcellular localization of pathology articulated by Dr. Gunnar Gouras, whose "inside- out" paradigm fundamentally challenges the extracellular dogma. Rather than Aβ plaques initiating disease through extracellular toxicity, Gouras demonstrates that Alzheimer's disease initiates within the synaptic endosome—a specialized endosomal compartment housed within the presynaptic terminal—where intraneuronal Aβ42 accumulation drives the earliest pathological changes. This framework integrates both lipid peroxidation and retromer dysfunction while explaining why extracellular therapeutics fail and establishing the mechanistic case for intracellular interventions. Intraneuronal Aβ42 at the Synaptic Endosome: The Subcellular Locus of Pathology The detection of intraneuronal amyloid-beta has historically been dismissed as an artifact of tissue processing or interpretation. However, advanced immunological methods, particularly synaptosomal flow cytometry and immuno-electron microscopy (EM), have conclusively established that Aβ42 —but not Aβ40—accumulates within intracellular compartments, particularly synaptic endosomes, decades before extracellular plaque formation occurs. This intraneuronal Aβ42 accumulation is not incidental to disease pathogenesis; rather, it represents the earliest detectable subcellular pathological change and a direct driver of subsequent neuronal dysfunction. The synaptic endosome is a specialized endosomal compartment housed within the presynaptic terminal, approximately 0.5-2.0 micrometers from the synaptic vesicle active zone. This compartment is critical for synaptic vesicle recycling, neurotransmitter receptor trafficking, and the regulation of synaptic strength. The synaptic endosome accomplishes this through high-frequency endocytosis and exocytosis cycles, with an

estimated 50-100 endocytosis events per second at a single active synapse during sustained neuronal activity. Intraneuronal Aβ42 accumulates selectively at the synaptic endosome through a process intimately linked to APP endocytosis and retromer dysfunction. APP, an integral membrane protein essential for normal neuronal function, undergoes continuous endocytosis at the synaptic terminal. Within the early endosome, APP is cleaved by β-secretase (BACE1) and subsequently by γ-secretase to generate Aβ peptides. Under normal conditions, the retromer complex rapidly recycles the remaining APP C- terminal fragments (CTFs) back to the plasma membrane or trans-Golgi network, limiting endosomal dwell time and preventing excessive intracellular Aβ generation. When retromer function is impaired—whether through direct SORL1/VPS35 mutations, ApoE4-mediated trafficking dysfunction, or other mechanisms— APP accumulates within enlarged, dysfunctional synaptic endosomes. Within this compartment, APP encounters elevated concentrations of both BACE1 and γ-secretase, dramatically increasing Aβ generation. The Aβ42 peptide, with its hydrophobic C-terminal extension, preferentially aggregates within the lipid-rich endosomal lumen, forming oligomeric and protofibrillar species. These intracellular Aβ42 oligomers directly interfere with synaptic vesicle recycling, impair SNARE protein function, disrupt vesicular trafficking, and trigger localized oxidative stress. Four-Phase Pathological Progression: From Intraneuronal Aβ to Neuritic Dystrophy The intraneuronal Aβ42 accumulation initiates a stereotyped four-phase progression of synaptic pathology. Understanding these phases is critical for appreciating why interventions targeting late-stage pathology fail and why early, intracellular interventions are mechanistically necessary. Phase 1 - Intraneuronal Aβ42 Accumulation and Synaptic Endosomal Dysfunction (Preclinical, ~10-20 years before symptom onset): Intraneuronal Aβ42 accumulates within synaptic endosomes of neurons in the lateral entorhinal cortex and other early-vulnerable regions. This phase is entirely intraneuronal and precedes any extracellular pathology. Synaptic endosomes become enlarged and dysfunctional, impairing normal recycling of synaptic vesicle proteins and neurotransmitter receptors. Biomarkers of this phase include elevated CSF phosphorylated tau (pTau181, pTau217), which reflects the kinase dysregulation consequent to impaired synaptic plasticity signaling, and decreased CSF Aβ42, which reflects the intraneuronal sequestration. Synaptic density begins to decline in vulnerable circuits, detectable via synaptosomal PET imaging or advanced MRI sequences. Phase 2 - Synaptic Failure and Local Tau Hyperphosphorylation (Preclinical/Early Symptomatic, ~5-15 years before cognitive symptoms): Impaired synaptic endosomal trafficking progressively starves synapses of essential proteins required for synaptic plasticity, strength maintenance, and long-term potentiation. Local kinase dysregulation—consequent to both impaired Reelin-ApoER2-Dab1 signaling (as detailed in Chapter 1) and stress-activated kinases responding to intraneuronal Aβ42 accumulation— drives hyperphosphorylation of tau at the synapse. Tau hyperphosphorylation destabilizes microtubules, impairs axonal transport, and initiates the formation of tau oligomers and early neurofibrillary tangle pathology. Synaptic loss accelerates. Cognitive symptoms begin to emerge as synaptic density falls below critical thresholds in allocentric encoding circuits. Phase 3 - Neuritic Dystrophy and Intraneuronal Tau Aggregation (Symptomatic, concurrent with mild cognitive impairment): Progressive tau

hyperphosphorylation and intraneuronal Aβ42 accumulation converge to drive severe cytoskeletal destabilization. Dendritic spines collapse, and neurites become grossly dystrophic—swollen, disorganized structures filled with accumulated phosphorylated tau, β-CTF, and Aβ oligomers. These dystrophic neurites form the anatomical substrate of the "neuritic plaques" observed in histology. Extracellular amyloid plaques emerge as a consequence of neuritic dysfunction and cellular lysis, not as a cause. Neuritic dystrophy is characterized by microtubule bundle disorganization, loss of normal mitochondrial positioning, and impaired axonal transport. Phase 4 - Neuronal Death and Tau Spread (Dementia stage): Progressive neuritic dystrophy culminates in neuronal death and cellular lysis. As dystrophic neurons lyse, they release their accumulated Aβ, tau, and other proteins into the extracellular space. This release drives both the emergence of extracellular amyloid plaques and the exosomal-mediated trans-synaptic spread of tau to downstream-connected neurons. The disease propagates anatomically according to connectional pathways, with pathology advancing from the lateral entorhinal cortex through the hippocampus and into cortical association areas. Widespread synaptic loss and neuronal death correlate with dementia severity. This four-phase model explains why anti-amyloid monoclonal antibodies, administered at the symptomatic stage (phases 3-4), fail to arrest cognitive decline: the pathological process is no longer fundamentally driven by intraneuronal Aβ42 but has progressed to tau aggregation, neuritic dystrophy, and neuronal death. Intervention at phase 1 (intraneuronal Aβ42 accumulation, preclinical) would theoretically prevent all downstream pathology, while intervention at phase 3-4 addresses only a consequence of the underlying disease. Table: Four-Phase Pathological Progression Phase Primary Pathology Subcellular Locus Biomarkers Symptomatolo gy Timeline Phase 1 Intraneuronal Aβ42 accumulation in synaptic endosomes Synaptic endosome (presynaptic) pTau181/pTau2 17 in CSF; Aβ42 in CSF; reduced synaptic density Asymptomatic 10-20 years pre- symptom Phase 2 Synaptic failure; local tau hyperphosphoryl ation; early tangle formation Synaptic compartment; dendritic spine pTau; phospho-tau in tau oligomers; synaptic density; FDG-PET in allocentric circuits Asymptomatic or subtle cognitive changes; possible MCI on retrospective assessment 5-15 years pre- symptom Phase 3 Neuritic dystrophy; extensive tau aggregation; extracellular plaque emergence Dendritic spines; neurites; extracellular space Extracellular Aβ plaques (PET imaging); pTau; widespread neuritic pathology on EM Mild-to- moderate cognitive impairment (MCI to mild dementia) 0-5 years into symptom stage Phase 4 Neuronal death; tau spread via exosomes; widespread plaque burden Extracellular space; trans- synaptic pathways; dying neurons Widespread amyloid and tau PET positivity; severe neuronal loss on MRI; CSF markers plateau Moderate-to- severe dementia 5+ years into symptom stage Outside-In Versus Inside-Out: A Comparative Critique The classical amyloid cascade hypothesis posits an "outside-in" disease mechanism: extracellular Aβ plaques trigger neurotoxicity through incompletely understood mechanisms, potentially involving microglial activation, complement activation, or direct synaptic toxicity. This toxicity then causes tau hyperphosphorylation, synaptic loss, and neuronal death. The evidence supporting this model is primarily correlative: amyloid plaques are present in AD brains, and amyloid mutations cause familial AD. However, the outside-in model suffers from several fatal

conceptual and empirical weaknesses. First, the anatomical dissociation between amyloid and tau pathology is profound: amyloid-beta PET imaging often identifies amyloid in cognitively normal elderly individuals and across widespread cortical regions, yet these individuals remain cognitively intact. In contrast, tau pathology is far more anatomically restricted, correlates tightly with cognitive decline, and predicts future cognitive symptoms. Second, the correlation between extracellular amyloid burden and cognitive impairment is poor ($r < 0.40$ in most studies), whereas the correlation between tau burden and cognitive decline is strong ($r > 0.75$). Third, anti-amyloid monoclonal antibodies dramatically reduce amyloid burden but produce marginal cognitive benefits (12-35% slowing of decline, not arrest or reversal), suggesting that amyloid clearance addresses a consequence rather than a cause. The inside-out framework articulated by Gouras inverts this causal architecture: disease initiates intracellularly with Aβ42 accumulation within the synaptic endosome, driven by retromer dysfunction and ApoE4-mediated trafficking impairment. This intraneuronal Aβ42 directly triggers local kinase dysregulation, cytoskeletal destabilization, and tau hyperphosphorylation. As pathology progresses, neuritic dystrophy and neuronal death release accumulated proteins into the extracellular space, creating the extracellular plaques observed in late-stage disease. Extracellular amyloid is thus a secondary consequence of intracellular pathology, not the driver. The inside-out model explains the empirical observations that the outside-in model cannot: (1) Why amyloid burden correlates poorly with cognition; (2) Why amyloid-clearance therapeutics fail; (3) Why tau pathology correlates tightly with cognitive decline; (4) Why intraneuronal Aβ42 precedes extracellular plaques by decades; (5) Why early AD selectively affects anatomically circumscribed regions with particular connectivity and trafficking characteristics; and (6) Why PET imaging shows amyloid in cognitively normal elderly individuals—they are in phase 1 of disease, with intraneuronal pathology not yet translated into synaptic failure. ApoE4-Aβ Intersection Within Endosomes: The Molecular Nexus The convergence of ApoE4 and Aβ within the synaptic endosome reveals the molecular nexus integrating the lipid peroxidation, retromer, and inside-out hypotheses. ApoE is trafficked into neurons via the apolipoprotein receptors (ApoER2, LRP1) and is internalized into early endosomes. Within the endosomal compartment, ApoE encounters APP and its fragments, as well as nascent Aβ peptides. In normal conditions, ApoE2 and ApoE3, with their protective disulfide-bonded oligomeric structures, compartmentalize Aβ and prevent its aggregation. The lipid-associated ApoE also regulates intracellular lipid trafficking and mitochondrial dynamics, protecting against oxidative stress. ApoE4, lacking disulfide bonds and existing primarily in a monomeric state, fails to compartmentalize Aβ and paradoxically promotes Aβ aggregation through direct protein-protein interactions. Furthermore, ApoE4 impairs endosomal trafficking efficiency, synergizing with retromer deficiency to amplify the endosomal dysfunction. At the molecular level, ApoE4 binds with altered kinetics to heparan sulfate proteoglycans on the endosomal membrane, reducing its interaction with normal recycling machinery. This creates a "double hit" scenario: retromer deficiency impairs trafficking efficiency, and ApoE4 additionally compromises the remaining trafficking capacity, creating a more severe endosomal trafficking bottleneck in ApoE4 carriers. The intraneuronal accumulation of Aβ42 in ApoE4 carriers is

approximately 2.5-3.0-fold greater than in ApoE3 carriers at equivalent disease stages, and ApoE4-associated intraneuronal Aβ shows greater propensity for oligomerization and protofibril formation. This molecular intersection— ApoE4-mediated trafficking dysfunction amplifying Aβ42 accumulation— explains the striking epidemiological dominance of ApoE4 in sAD pathogenesis. PANTHOS Integration: Somatic Versus Synaptic Aβ Distinction PANTHOS (Greek, "poisonous anthos [flower]") is the terminal perikaryal morphology of autophagic–lysosomal failure named by Lee, Nixon, and colleagues (2022): a neuron so swollen with de-acidified, Aβ42-filled autolysosomes that its cargo arranges into flower-like rosettes around the cell body. In amyloid precursor protein (APP) transgenic mouse models, quantitative analysis identified these individual PANTHOS neurons as the principal source of senile plaques; the same morphology is observed in human AD brain, though its fractional contribution to human plaque burden has not been quantified. Because PANTHOS is intrinsically a somatic (perikaryal) event, it anchors the distinction drawn here between somatic (neuronal cell body) and synaptic Aβ accumulation. While both compartments exhibit intraneuronal Aβ42 accumulation in early disease, the functional consequences differ substantially. Synaptic Aβ42 accumulation (housed within synaptic endosomes) directly impairs synaptic plasticity, neurotransmitter receptor trafficking, and synaptic vesicle recycling. Even modest synaptic Aβ42 accumulation (10-50 nanomolar local concentrations) disrupts long-term potentiation, reduces dendritic spine density, and triggers local kinase dysregulation driving tau hyperphosphorylation. Synaptic pathology manifests as synaptic loss detectable via multiple modalities: dendritic spine density reduction on electron microscopy, loss of synaptic vesicle markers (synaptophysin, SNAP-25), and impaired glucose metabolism detectable on PET imaging. Somatic Aβ42 accumulation (within the perikaryal endosomal-lysosomal system) represents a later pathological event, occurring after synaptic compartments are profoundly affected. Somatic Aβ contributes to oxidative stress, energy depletion, and mitochondrial dysfunction but is less directly disruptive to memory-encoding computations. The distinction is mechanistically important: therapeutic interventions targeting synaptic Aβ42 accumulation—via enhancing retromer function, restoring ApoER2 signaling, or stabilizing synaptic endosomal integrity—would theoretically be effective if administered during phases 1-2. Interventions administered at phase 3-4, after extensive neuritic dystrophy and somatic Aβ accumulation have occurred, address a consequence rather than a cause. Volloch ACH2.0 and T1 Threshold: Mechanisms of Intracellular Aβ42 Toxicity Recent structural and biophysical characterization of intraneuronal Aβ42 oligomers has revealed their mechanism of toxicity at the subcellular level. The Volloch ACH2.0 model (Aβ42 Conformational Heterogeneity 2.0) describes the structural properties of Aβ42 within the lipid-rich, acidic environment of the synaptic endosome. Unlike extracellular Aβ42, which preferentially forms fibrillar structures stabilized by cross-β architecture, endosomal Aβ42 forms transient oligomers stabilized through hydrophobic burial and electrostatic interactions with the acidic lipid bilayer. These endosomal Aβ42 oligomers exhibit a T1 threshold—a critical concentration above which their toxicity exponentially increases. This threshold, approximately 20-50 nanomolar within the endosomal lumen, represents the concentration at which oligomeric species transition from monomeric

equilibrium to nucleation-driven polymerization. Below the T1 threshold, oligomers are transient and partially reversible. Above it, oligomerization becomes explosive and irreversible. The T1 threshold is particularly relevant to understanding phase transitions in disease: early disease represents a state where Aβ42 concentrations hover near or slightly below the T1 threshold, creating a metastable, potentially reversible pathological state. As disease progresses and Aβ42 accumulates further, passage through the T1 threshold commits the neuron to a more severe, irreversible degenerative pathway. Trans-Synaptic Seed Propagation: From Intracellular to Network Pathology While the inside-out framework emphasizes intraneuronal pathology as the primary driver, it does not negate trans-synaptic propagation of pathology. Rather, it reframes propagation as a secondary consequence occurring after sufficient intraneuronal pathology has accumulated. The mechanism is as follows: As intraneuronal Aβ42 accumulation progresses within phase 1-2, neuritic stress and the prodromal metabolic changes activate exosomal release pathways. Synaptic endosomes progressively mature into multivesicular bodies, packaging accumulated Aβ42 and tau into intraluminal vesicles. When these multivesicular bodies fuse with the plasma membrane, they release exosomes containing Aβ42 and phosphorylated tau into the synaptic cleft. These exosomes are recaptured by postsynaptic partners or diffuse to engage neighboring neurons. The recaptured exosomal cargo is endocytosed into the recipients' synaptic endosomes, "seeding" the accumulation in downstream-connected neurons. This trans-synaptic spread progresses along connectional pathways: from the lateral entorhinal cortex to the hippocampus, then to temporal association cortex, and finally to prefrontal and parietal cortices, following the known anatomical progression of Braak staging. The spread is not autonomous—not every neuron receiving exosomal tau becomes pathological. Rather, neurons with existing vulnerabilities (high endosomal trafficking burden, ApoE4 genotype, previous oxidative stress) are preferentially susceptible. This explains why disease progression is relatively stereotyped yet variable between individuals. Why Lecanemab and Donanemab Cannot Access Intracellular Aβ The failure of monoclonal antibodies targeting amyloid-beta to meaningfully arrest cognitive decline becomes transparent within the inside-out framework. Both lecanemab and donanemab are large immunoglobulin molecules (~150 kilodaltons) that cannot cross the blood-brain barrier in significant quantities; their CNS penetration is extremely limited even with the disrupted BBB present in advanced AD. More fundamentally, these antibodies target extracellular Aβ, which by the time cognitive symptoms emerge (phase 3-4), is largely a consequence of neuronal death and lysis. The pathological driver—intraneuronal Aβ42 accumulation within the synaptic endosome—remains inaccessible to these extracellular antibodies. True disease modification would require interventions that preserve synaptic endosomal homeostasis and prevent intraneuronal Aβ42 accumulation during phases 1-2, years to decades before cognitive symptom onset. Such interventions would necessarily be intracellular in their site of action. These include: (1) Retromer stabilization via pharmacological chaperones or RhoGEF12 inhibitors; (2) ApoE4-targeted interventions reducing endosomal trafficking dysfunction; (3) SORL1 gene therapy restoring endosomal cargo sorting capacity; or (4) Interventions targeting the kinase cascades (GSK3β, LIMK1, Cdk5) that drive tau hyperphosphorylation downstream

of endosomal dysfunction. The inside-out paradigm thus establishes that the appropriate temporal window for intervention is preclinical, and the appropriate spatial locus is intracellular, specifically the synaptic endosome. This represents a fundamental departure from the extracellular, symptomatic-stage approach that has dominated the field for decades. --- Figure 3.1: Convergence of AD Pathology within the Synaptic Endosome. APP is internalized from the plasma membrane into early endosomes where BACE1 generates Aβ42, which accumulates on MVB membranes. ApoE4 variants exhibit impaired recycling, causing endosomal enlargement.

4. The Chronic Excitatory Insufficiency Hypothesis

(Moosmann and Sohre) Introduction and Network Integration The preceding three chapters examined distinct molecular mechanisms— lipid peroxidation, endosomal trafficking, and intracellular Aβ42 accumulation—each providing mechanistic insight into specific pathological cascades. This chapter synthesizes these mechanisms within the larger framework of network-level homeostasis, specifically the "Chronic Excitatory Insufficiency" (CEI) hypothesis articulated by Bernd Moosmann and Selina Sohre. A 2026 primary-literature fact-check (recorded at CORRECTIONS C-016, with the graded verdict in the concept note *Chronic Excitatory Insufficiency*) places CEI as a refuted, dormant minority provocation: its individual citations are largely faithful, but its load-bearing inversion is contradicted by the direction of the anti-amyloid trials—amyloid *removal* slows decline—and by human-brain-derived Aβ oligomers that are synaptotoxic at low-nanomolar concentrations, while the underlying preprint remains unpeer-reviewed and effectively uncited. It is retained here as a graded contrast case rather than an endorsed framework: a fair map of the field carries its strongest inversion so the corpus can state precisely why it does not hold. The CEI hypothesis inverts canonical dogma: rather than positing that Aβ plaques and tau tangles are the proximate neurotoxic drivers of neurodegeneration, it argues that these molecular hallmarks represent desperate, physiologically maladaptive compensatory responses to a primary deficit in glutamatergic excitatory neurotransmission. This framework reconceptualizes Alzheimer's disease as fundamentally a homeostatic network failure—an inability to maintain excitatory-inhibitory (E/I) balance—where Aβ and tau are symptoms of this underlying deficit rather than causes. Molecular Convergence of Risk Factors on NMDA Receptor Function The CEI hypothesis derives its rhetorical power from unifying seemingly disparate genetic and environmental risk factors through a single convergence point: N-methyl-D-aspartate (NMDA) receptor function and glutamatergic signaling. That each factor *touches* glutamatergic signaling is real; that this is the *only* shared proximate node is not—endosomal–lysosomal–autophagy dysfunction (Nixon) and APP/Aβ processing are at least equally strong convergence points across the same factors, and CEI excludes amyloid only by pre-declaring it compensatory, which is circular. The convergence is therefore best read as *a* recurring node, not the sole one. By systematically analyzing how diverse AD risk factors—ApoE4, Presenilin-1 mutations, Trisomy 21, mechanical neurotrauma, estrogen loss, and immune dysregulation— converge upon NMDA

receptor signaling, the hypothesis demonstrates exceptional structural and explanatory robustness. ApoE4 and NMDA Receptor Trafficking. ApoE4, in addition to its effects on endosomal trafficking and lipid peroxidation, directly impairs NMDA receptor trafficking and synaptic localization. Synaptic NMDA receptors are trafficked to and maintained at synaptic sites through interactions with PSD95 (postsynaptic density protein 95) and other scaffold proteins. ApoE4, through its altered lipoprotein domain properties and enhanced association with endosomal compartments, sequesters NMDA receptors in intracellular endosomal compartments, reducing their synaptic availability. This reduces NMDA-mediated calcium influx, impairing synaptic plasticity and CREB- dependent gene transcription. Presenilin-1 Mutations and γ-Secretase Function. Familial AD mutations in PSEN1 (encoding presenilin-1, the catalytic subunit of γ-secretase) alter γ- secretase activity in ways that elevate Aβ42 production. However, PSEN1 also mediates the cleavage of Notch, a developmental signaling molecule critical for dendritic complexity and synaptogenesis. Mutant PSEN1 impairs Notch processing, reducing dendritic development and synaptic density. Furthermore, presenilin-1 regulates intracellular calcium homeostasis through its interaction with the inositol 1,4,5-trisphosphate (IP3) receptor. Mutant presenilin-1 impairs calcium store release and contributes to altered glutamatergic signaling. These presenilin effects operate independently of amyloid production, explaining why presenilin mutations cause familial AD at ages younger than amyloid mutations and with higher penetrance. Trisomy 21 and Glutamatergic Imbalance. Trisomy 21 (Down syndrome) individuals possess three copies of chromosome 21, which encodes the APP gene, DYRK1A kinase, and other genes affecting excitatory-inhibitory balance. The triplication of APP increases Aβ production, but simultaneously, triplication of DYRK1A and other chromosome 21 genes impairs excitatory synaptic development and increases GABAergic inhibition. The net result is a profound excitatory insufficiency beginning early in development and progressing throughout life. Down syndrome individuals develop clinical and neuropathological AD by their 40s-50s, making them an extraordinarily informative natural experiment in accelerated neurodegeneration. The CEI framework explains this: the primary deficit is the excitatory insufficiency (from DYRK1A triplication and other factors), while Aβ elevation (from APP triplication) is an attempted compensatory response. Mechanical Neurotrauma. Traumatic brain injury (TBI) is an established risk factor for later-life AD, with meta-analytic risk ratios of 1.5-2.0. The acute phase of TBI involves massive glutamate release from damaged axons and excitotoxicity, but the chronic phase involves profound excitatory insufficiency as glutamatergic terminals are lost and their axons damaged. The chronically injured brain exhibits reduced synaptic density, impaired long-term potentiation, and deficient glutamatergic signaling. The increased Aβ production observed in post-TBI cohorts may represent a compensatory attempt to restore excitatory tone. Estrogen Loss and Menopausal Transition. Estrogen is a critical neuromodulator enhancing NMDA receptor function, promoting dendritic spine maturation, and supporting glutamatergic neurotransmission. At menopause, the precipitous decline in circulating estrogen impairs glutamatergic signaling and contributes to accelerated cognitive aging in women. Women face a 2-3-fold elevated AD risk compared to men of similar age, substantially attributable to

menopausal estrogen loss. The increased Aβ and tau pathology observed in postmenopausal women may reflect compensatory responses to estrogen-loss-induced excitatory insufficiency. TREM2, BIN1, and SORL1 in Innate Immunity. TREM2 (triggering receptor expressed on myeloid cells 2), a microglial receptor, regulates phagocytic capacity and microglial morphology. In addition to immune functions, TREM2 signaling in neurons modulates synaptic plasticity through NMDA receptor regulation. TREM2 loss-of-function variants impair NMDA- dependent synaptic plasticity independent of immune effects. Similarly, BIN1 and SORL1, while classically implicated in endosomal trafficking, also regulate dendritic spine structure and synaptic excitatory tone. These pleiotropic effects on glutamatergic signaling unite immune and synaptic dysfunction aspects of AD within the excitatory insufficiency framework. Table: Risk Factors for AD and Their Convergence on Glutamatergic- NMDA Signaling Risk Factor Mechanism of NMDA/Glutamatergic Impairment Primary vs. Compensatory Aβ/Tau ApoE4 genotype NMDA receptor sequestration in endosomes; reduced synaptic localization; impaired CREB signaling Primary: excitatory insufficiency; Secondary: Aβ/tau as compensation PSEN1 mutations (familial AD) Impaired Notch signaling; altered calcium homeostasis; reduced dendritic development Primary: developmental synaptogenic deficit; Secondary: Aβ elevation compensatory Trisomy 21 (Down syndrome) DYRK1A triplication increases inhibition; APP triplication increases Aβ Primary: E/I imbalance; Secondary: Aβ as compensation for DYRK1A effects Mechanical neurotrauma (TBI) Axonal damage; glutamatergic terminal loss; impaired LTP Primary: physical loss of glutamatergic capacity; Secondary: Aβ as restoration attempt Estrogen loss (menopause) Impaired NMDA receptor function; reduced dendritic spine maturation Primary: neuromodulatory deficit; Secondary: Aβ/tau as compensation TREM2 loss-of-function Impaired NMDA-dependent synaptic plasticity; altered microglial support for glutamate homeostasis Primary: synaptic plasticity deficit; Secondary: Aβ/tau as compensation BIN1/SORL1 loss-of-function Reduced dendritic spine stability; impaired synaptic AMPA/NMDA Primary: synaptic structural deficit; Secondary: Aβ/tau as compensation trafficking Phenotypic Manifestations: Cognitive and Non-Cognitive Symptoms The CEI hypothesis predicts specific phenotypic consequences of progressive glutamatergic insufficiency that extend beyond memory loss. These predictions align remarkably with the non-cognitive symptoms long recognized in AD but poorly explained by the amyloid cascade hypothesis. Learning and Memory Dysfunction. The hippocampus and cortical circuits mediating episodic memory depend critically on NMDA receptor-dependent synaptic plasticity and long-term potentiation. NMDA receptors act as synaptic coincidence detectors: calcium influx through NMDA channels is required for the post-translational modifications (particularly the phosphorylation and insertion of AMPA receptors into the postsynaptic membrane) that underlie memory consolidation. Chronic glutamatergic insufficiency progressively impairs this capacity, resulting in the profound anterograde amnesia and difficulty learning new information characteristic of AD. The CEI framework predicts that interventions enhancing NMDA function would benefit learning and memory—a prediction borne out by the clinical efficacy of memantine, an uncompetitive NMDA antagonist that paradoxically improves cognition through selective unblocking of tonically activated NMDA

receptors (discussed later). Sleep Fragmentation and Architectural Abnormalities. AD patients experience characteristic sleep disturbances: increased sleep fragmentation, shortened slow-wave sleep duration, and altered circadian rhythm architecture. These sleep abnormalities are driven by glutamatergic insufficiency affecting the suprachiasmatic nucleus (SCN) and other sleep- wake regulatory circuits. The SCN maintains circadian rhythmicity through NMDA-dependent glutamatergic signaling from the retinohypothalamic tract. Impaired NMDA signaling disrupts circadian phase-locking and reduces slow-wave sleep, driving the sleep-wake fragmentation observed clinically. Sleep loss itself exacerbates Aβ and tau pathology, creating a vicious cycle whereby excitatory insufficiency drives poor sleep, which increases pathological protein accumulation, which further impairs excitatory function. Hearing Loss. High-frequency sensorineural hearing loss is an early, often- overlooked feature of AD, present in up to 80% of AD patients and preceding cognitive symptom onset by years. The cochlear nucleus and auditory cortex depend critically on intact glutamatergic synaptic transmission mediated by AMPA and NMDA receptors. Glutamatergic insufficiency progressively impairs auditory synaptic function, manifesting as sensorineural hearing loss. The frequency-selective nature of AD- associated hearing loss (preferential high-frequency loss) mirrors the pattern of glutamatergic terminal loss, which affects frequency-selective auditory circuits preferentially. Seizures and Hyperexcitability. AD carries a markedly elevated seizure risk (subclinical epileptiform activity in roughly 40% of patients; clinical seizures in ~10–20%, higher still in early-onset autosomal-dominant and Down-syndrome forms) against a <1% population baseline. Moosmann's CEI derives this counter-intuitively from an inhibition-dominant network, in which the sparse surviving excitatory signals are pathologically over-amplified against an over-inhibited background—the mechanism established for silent/absence seizures (Klaassen et al., 2006; Cope et al., 2009). This is a genuine but minority reading. The better-supported account of Alzheimer's seizures—and the one this corpus adopts—runs in the opposite polarity: the progressive loss of parvalbumin-positive fast-spiking GABAergic interneurons disinhibits the network, and restoring inhibition (e.g., via Nav1.1) rescues the phenotype (Verret et al., 2012; Palop & Mucke, 2016), while low-dose levetiracetam, which lowers excitability, improves function in amnestic mild cognitive impairment (Bakker et al., 2012). The two accounts lay claim to the same epileptiform datum through opposite-signed mechanisms; the corpus resolves them by epoch—compensated hypo-excitation early, decompensated disinhibition at the terminus—and does not attribute the disinhibition mechanism to CEI. Psychiatric Symptoms and Apathy. Behavioral and psychiatric manifestations of AD—including depression, anxiety, apathy, and behavioral disinhibition—are thought to reflect pathology in prefrontal cortex, anterior cingulate, and limbic circuits regulating mood and motivation. These circuits depend critically on intact glutamatergic and dopaminergic neurotransmission. Glutamatergic insufficiency impairs prefrontal function, contributing to apathy, reduced motivation, and behavioral abnormalities. The apathy phenotype specifically reflects dopaminergic insufficiency secondary to reduced glutamatergic drive on dopaminergic neurons. Glutamate-dopamine interactions are critical for reward processing and behavioral motivation; loss of glutamatergic input to midbrain dopaminergic

systems impairs motivation and drives the apathetic phenotype. Allostatic Burden: The Cumulative Stress of Compensatory Mechanisms The CEI hypothesis employs the concept of "allostatic burden"—the cumulative physiological cost of adaptive responses to chronic stress. In the context of AD, chronic glutamatergic insufficiency triggers multiple compensatory mechanisms: increased Aβ production attempting to enhance excitability, tau hyperphosphorylation and aggregation attempting to enhance microtubule stability and cellular transport, and upregulation of intrinsic neuronal excitability. These compensatory responses are initially protective but become increasingly maladaptive as they accumulate. Aβ as Glutamatergic Sensitizer. Aβ oligomers, at subacute concentrations (10-100 nanomolar), potentiate NMDA receptor function and enhance glutamatergic synaptic transmission. At these concentrations, Aβ represents a compensatory response to glutamatergic insufficiency, functioning as an endogenous glutamatergic sensitizer. This explains why early intraneuronal Aβ accumulation correlates with preserved cognition (phase 1) and why Aβ elevation is observed in cognitively normal elderly individuals—the Aβ is providing compensatory enhancement of weakened glutamatergic transmission. However, as Aβ accumulates further, exceeding the T1 threshold, it transitions from compensatory to neurotoxic, directly impairing synaptic function and overwhelming the neuron. Tau as Structural Sensitization. Tau hyperphosphorylation initially represents a compensatory attempt to enhance microtubule stability and axonal transport capacity in neurons experiencing energy depletion and impaired mitochondrial function consequent to glutamatergic insufficiency. Enhanced tau phosphorylation increases microtubule bundle stability and enhances fast axonal transport, partially compensating for reduced ATP availability. However, this compensation is temporary and comes at great cost: tau hyperphosphorylation destabilizes the microtubule lattice, impairs kinesin motor function, and eventually leads to tau aggregation. The transition from compensatory tau hyperphosphorylation to pathological tau aggregation represents the point at which the allostatic burden becomes unsustainable. The Hibernation Model. An integrative concept explaining the chronic excitatory insufficiency is the "hibernation model": neurons chronically deprived of glutamatergic input progressively downregulate activity to conserve limited energy resources. This metabolic downregulation— reduced dendritic complexity, spine loss, mitochondrial dysfunction— mirrors the energy conservation strategies employed by hibernating mammals. While adaptive in the short term, chronic hibernation leads to skeletal wasting, immune impairment, and eventual death. Similarly, neurons in chronic hibernation due to glutamatergic insufficiency experience progressive atrophy, reduced capacity for plasticity, and eventual death. Cell-Cycle Re-entry and Arendt's "Dr. Jekyll and Mr. Hyde" Model. Thomas Arendt proposed that neurons in AD undergo pathological cell-cycle re-entry —reactivation of molecular programs normally associated with cell division. This re-entry is triggered by energy depletion and bioenergetic failure consequent to reduced glutamatergic input. Neurons attempt to restore energy by reactivating metabolic programs associated with growth, but this simultaneously activates apoptotic pathways. The result is a tragic paradox: the neuron simultaneously upregulates growth-associated kinases (CDKs) and apoptotic caspases, driving tau hyperphosphorylation (via CDK activation) and neuronal death (via caspase

activation). This "Dr. Jekyll and Mr. Hyde" scenario reflects the maladaptive nature of cell-cycle re-entry in terminally differentiated neurons. Resolving the Memantine Anomaly: E/I Balance and PV+ Interneuron Selectivity One of the most challenging anomalies in AD therapeutics is the paradoxical efficacy of memantine. Memantine is an uncompetitive NMDA receptor antagonist, and according to the amyloid cascade hypothesis, blocking NMDA receptors should exacerbate neurodegeneration by further reducing glutamatergic function. Yet memantine demonstrates modest but consistent cognitive benefits in moderate-to-severe AD patients, with effect sizes of approximately 12-25% slowing of cognitive decline. The CEI hypothesis resolves this paradox through the lens of inhibitory tone and parvalbumin-positive GABAergic interneuron function. In chronic excitatory insufficiency, GABAergic inhibitory neurons—particularly parvalbumin-positive fast-spiking interneurons critical for feedforward and feedback inhibition—become hyperexcitable due to compensatory mechanisms. These interneurons depend critically on tonic, background NMDA receptor-mediated excitation provided by glutamate spillover from neighboring glutamatergic synapses. In excitatory insufficiency, this tonic NMDA drive is reduced, but the interneurons compensate by increasing their intrinsic excitability and their contribution to the inhibitory tone. Memantine, by selectively blocking tonic NMDA current while preserving phasic (event-driven) NMDA transmission, preferentially suppresses the tonic excitation of parvalbumin interneurons. This reduces inhibitory tone, relieving the brake on pyramidal neuron firing. The net effect is enhancement of pyramidal neuron activity and improved memory- dependent computation despite net NMDA receptor blockade. Remarkably, memantine achieves this through a subtle pharmacological principle: uncompetitive, voltage-dependent channel blockade preserves the ability of high-concentration glutamate transients (associated with actual synaptic transmission) to briefly dislodge the blocker, while preventing low- concentration glutamate background (tonic, extrasynaptic NMDA current) from driving continuous channel activity. This mechanism predicts that memantine efficacy depends critically on the integrity of parvalbumin-positive interneuron populations. In advanced AD, when parvalbumin interneurons are substantially lost, memantine efficacy diminishes—a prediction borne out by clinical observation. Furthermore, this framework suggests that future therapeutic strategies might involve selective GABAergic inhibition (through GABA-A antagonists or interneuron- selective enhancement of glutamate) as a more direct approach than memantine's dual NMDA modulation.

Therapeutic Implications and the Case for E/I-Targeting Interventions

The chronic excitatory insufficiency hypothesis dictates fundamentally different therapeutic approaches than the amyloid cascade paradigm. Rather than aggressive amyloid and tau clearance, the CEI framework prioritizes restoration of glutamatergic tone and excitatory-inhibitory balance. Candidate interventions include:

1. NMDA Receptor Enhancers and Partial Agonists. Compounds that enhance NMDA receptor signaling—such as positive allosteric modulators or partial agonists—would theoretically counteract the primary deficit. These agents would need selective targeting of hippocampal and cortical NMDA receptors while avoiding excitotoxic doses.

2. Glutamate Receptor Trafficking Enhancement. Interventions that enhance the synaptic localization of AMPA and NMDA receptors—through modulation of auxiliary proteins, kinases regulating phosphorylation, or enhancing PSD95 scaffolding—would increase glutamatergic synaptic strength independent of ligand supply.

3. Selective GABAergic Inhibition. Partial or selective GABAergic antagonism, targeting particularly parvalbumin interneurons or extrasynaptic GABA-A receptors, would increase the net excitatory output of glutamatergic circuits. This represents a logical extension of memantine's mechanisms.

4. Preservation of Glutamatergic Connectivity. Interventions supporting axonal health, reducing glutamatergic terminal loss, and enhancing presynaptic glutamate release capacity—through factors like neurotrophic factors (NGF, BDNF), mitochondrial support, or axonal transport enhancement—would directly address the primary deficit. The CEI hypothesis thus reframes AD therapeutics from a "cleanup" paradigm (removing Aβ and tau) to a "restoration" paradigm (preserving and enhancing glutamatergic signaling). This shift has profound implications for patient selection (early intervention when excitatory insufficiency is emerging), therapeutic timing (preclinical rather than symptomatic stages), and drug development priorities (excitatory enhancers rather than amyloid-targeting agents). --- END OF CHAPTERS Figure 4.1: Convergence of Alzheimer's Risk Factors on Excitatory Insufficiency. Primary risk factors independently degrade NMDA receptor surface expression and glutamatergic tone, converging on Chronic Excitatory Insufficiency as the central pathological bottleneck. Figure 4.2: The Biphasic Physiological Impact of Amyloid-Beta Concentration. At picomolar concentrations, Aβ enhances LTP; as chronic excitatory insufficiency forces prolonged overproduction, Aβ accumulates into the micromolar range, forming oligomers that trigger receptor internalization and synaptic depression. PART II Individual Framework Evaluations: Systemic and Neuroimmune Mechanisms Chapters 5–8

5. The Moosmann-Rappoport Synthesis: From Lipid

Rafts to Allostatic Collapse The preceding chapter examined Bernd Moosmann's revolutionary reframing of Alzheimer's disease as a consequence of chronic excitatory insufficiency rather than primary amyloid toxicity. This chapter now systematically evaluates Ari Rappoport's subsequent and complementary theoretical architecture—the Lipid-Raft and Adaptive Response Theory articulated in The Science of the Brain: Function, Dysfunction and Disease (2025). Whereas Moosmann identifies the functional epicenter of pathogenesis at the level of NMDA receptor dysfunction, Rappoport identifies the structural prerequisite: the degradation

of neuronal membrane lipid rafts. These theories are not competitive but deeply interdependent, constituting two temporal and causal facets of a unified pathological process. Lipid rafts are specialized microdomains of the neuronal plasma membrane that function as organizing platforms for synaptic receptor clustering, trafficking, and signaling. Composed of cholesterol, sphingolipids, and specific protein complexes, lipid rafts serve as the membrane-architectural scaffolding upon which NMDA receptors and numerous other synaptic proteins assemble and maintain their functional localization. Rappoport's critical insight involves demonstrating that diverse Alzheimer's disease risk factors—including ApoE4, traumatic brain injury, chronic inflammation, and age-related metabolic decay—all converge on a singular, initial pathological event: the structural degradation and functional destabilization of these lipid raft domains. This membrane pathology precedes and causally precipitates the NMDA receptor hypofunction that Moosmann identifies as proximate cause. The sequential integration of these models reveals a six-stage temporal and causal cascade. In Stage 1, genetic and environmental insults compromise lipid raft integrity through diverse mechanisms: ApoE4 impairs cholesterol homeostasis and alters raft-associated protein trafficking; traumatic brain injury causes mechanical disruption of membrane architecture; chronic inflammation triggers lipid peroxidation cascades; and age-related mitochondrial dysfunction compromises the energy-dependent synthesis and maintenance of membrane lipids. In Stage 2, lipid raft degradation directly disrupts the clustering and membrane trafficking of NMDA receptors, leading to severe depletion of surface NMDA receptor density. This represents the structural substrate for Moosmann's functional deficit. In Stage 3, profound glutamatergic insufficiency develops as a direct physiological consequence of reduced NMDA receptor availability and function. The brain's excitatory synapses are progressively denuded of their capacity to respond to glutamatergic stimulation, triggering widespread disruption of long-term potentiation, calcium influx, and CREB-dependent transcription. Stage 4 initiates the compensatory phase: the brain, detecting chronic excitatory insufficiency, activates a desperate homeostatic response through the upregulation of amyloid-beta production and tau hyperphosphorylation. These proteins, far from being pathogenic accidents, function as physiological glutamatergic sensitizers and synaptic stabilizers. At picomolar concentrations, amyloid-beta enhances NMDA receptor-dependent synaptic transmission, increases release probability, and facilitates long-term potentiation. Tau hyperphosphorylation facilitates axonal transport under cellular stress and sensitizes dendritic NMDA receptors. Stage 5 represents a period of partial compensation in which the brain maintains precarious equilibrium through sustained upregulation of these compensatory mechanisms. However, this equilibrium is neither indefinite nor stable; it represents an increasing allostatic load on the brain's homeostatic systems. Stage 6 constitutes allostatic collapse—the terminal failure of the compensatory response. The sustained production of amyloid-beta and hyperphosphorylated tau, while initially adaptive, becomes maladaptive through multiple mechanisms. Excessive amyloid-beta oligomerizes and aggregates, creating a thermodynamic sink that depletes the soluble monomer pool essential for synaptic plasticity. Tau aggregation into neurofibrillary tangles disrupts microtubular architecture and axonal transport irreversibly. Chronic neuroinflammation escalates secondary

to amyloid plaques and activated microglia. The brain's allostatic load—the cumulative physiological wear-and-tear from sustained compensatory activation—finally exceeds the system's capacity for self-regulation and repair. Cognitive decline accelerates, synapses are lost irreversibly, and neurodegeneration becomes manifest. The temporal sequencing embedded within this model resolves a profound historical paradox in Alzheimer's research: the decades-long lag between the appearance of amyloid pathology and the clinical onset of dementia. Asymptomatic individuals may harbor extensive amyloid plaques for ten to twenty years because amyloid-beta, in its compensatory role, is simultaneously preventing cognitive decline. Clinical symptoms emerge only when compensatory mechanisms fail and allostatic load exceeds critical thresholds. This timeline explains the failure of anti-amyloid therapeutics: ablating the very proteins that sustain compensatory function removes the brain's primary defense against underlying excitatory insufficiency, thereby accelerating cognitive decline—a phenomenon observed in certain clinical trials. Rappoport's integration of secondary genetic loci provides crucial mechanistic scaffolding for the lipid raft hypothesis. SORL1 (sortilin-related receptor 1) encodes a protein essential for NMDA receptor trafficking and internalization. ApoE4-driven dysfunction of SORL1-mediated endosomal recycling directly explains the intracellular trapping of NMDA receptors that Moosmann describes. BIN1 (bridging integrator 1) localizes to lipid raft microdomains and functions in clathrin-mediated endocytosis; its dysregulation compromises both membrane structure and receptor trafficking. PICALM (phosphatidylinositol binding clathrin assembly protein) similarly regulates membrane trafficking and endocytosis; genetic variants in PICALM impair the spatial organization of membrane domains and the internalization of raft-associated proteins. These secondary loci do not function as independent pathways but as components of an integrated membrane architecture and trafficking network whose dysfunction is precipitated by primary lipid raft degradation. Allostatic load theory provides the unifying theoretical framework integrating all these mechanistic components. Allostatic load represents the physiological cost of chronic activation of compensatory regulatory systems in the context of persistent environmental challenge. The brain facing chronic excitatory insufficiency enters a state of sustained activation of compensatory mechanisms—upregulation of amyloid-beta, tau hyperphosphorylation, mitochondrial stress, and glial activation. These compensatory responses incur biological costs: energy expenditure, oxidative stress, proteostatic burden, and inflammation. Over years and decades, these costs accumulate. The brain's capacity for repair and adaptation becomes progressively exhausted. The allostatic load exceeds what the system can sustain. At this point, compensatory mechanisms themselves become pathogenic, and neurodegeneration becomes irreversible. This conceptual framework carries profound implications for therapeutic strategy. If amyloid-beta and tau represent compensatory responses to upstream lipid raft and NMDA dysfunction rather than primary toxins, then therapeutic strategies aimed at ablating these proteins fundamentally misdiagnose the disease's nature. Such strategies address symptoms and pathological hallmarks while leaving the primary structural and functional deficits intact—or worse, removing the brain's primary defense against these deficits. A rational therapeutic approach would instead target lipid raft preservation and stabilization, NMDA receptor

trafficking and clustering, and the restoration of excitatory tone. Such interventions would reduce the allostatic load imposed on compensatory systems, allowing the brain's endogenous neuroprotective mechanisms to function adequately without becoming pathogenic themselves. The Moosmann-Rappoport synthesis thus redirects research away from protein ablation toward structural membrane preservation and functional glutamatergic restoration. --- Figure 5.1: Epistemological Shift in Alzheimer's Disease Etiology. The traditional Toxicopathy Paradigm assumes a linear path from toxic protein aggregation to neurodegeneration; the Compensatory Homeostatic Paradigm reframes Aβ and p-tau as physiological sensitizers induced by upstream deficits. Figure 5.2: Convergence of Disparate Triggers in the Excitatory Insufficiency Paradigm. The CEI model reconciles diverse genetic, developmental, and environmental risk factors through their shared suppression of glutamatergic signaling. Figure 5.3: Unified Compensatory Pathogenesis of Alzheimer's Disease. A synthesis of contemporary theoretical models showing the three-phase progression from lipid-raft disruption through NMDA hypofunction to allostatic exhaustion.

6. Synaptic Restriction and Proteostatic Collapse:

The Dual Margolis Models The Moosmann-Rappoport synthesis identified excitatory insufficiency and membrane pathology as fundamental drivers of neurodegeneration, yet important mechanistic gaps remained regarding the specific molecular executioners of synaptic loss and tau aggregation independent of amyloid pathology. Seth S. Margolis's research program fills this critical void through two complementary yet distinct mechanistic frameworks. The first elucidates the pathological reactivation of developmental synapse repression pathways in the adult diseased brain. The second identifies a novel, ubiquitin-independent protein degradation mechanism—the Neuronal Membrane Proteasome—that directly links ApoE4 genetic risk to tauopathy while bypassing amyloid intermediaries. Together, these contributions establish synaptic restriction and proteostatic collapse as autonomous neurodegenerative mechanisms that can operate independently from or in concert with amyloid pathology. The Ephexin5-RhoA Pathway represents the first major pillar of Margolis's work. Ephexin5 (ARHGEF15) is a guanine nucleotide exchange factor (GEF) that activates RhoA, a small GTPase critical for controlling dendritic spine structure and stability. During normal brain development, ephrin signaling through EphB2 receptors activates Ephexin5, which then activates RhoA to suppress the formation of excitatory synapses. This developmental synapse repression is essential for the process of neural circuit refinement: excess synaptic connections formed during development must be selectively eliminated to establish appropriate circuit architecture and computational capacity. Margolis demonstrated that in Alzheimer's disease, this developmental synapse repression program is pathologically reactivated in the adult brain—what might be termed a "perverted neurodevelopmental program." The molecular mechanism driving this reactivation involves EphB2 receptor depletion. Amyloid-beta oligomers bind directly to the fibronectin repeats domain of EphB2, a receptor tyrosine kinase

absolutely critical for NMDA receptor function and synaptic plasticity. This binding triggers proteasomal degradation of EphB2 itself. The loss of EphB2 is not merely a passive consequence of amyloid toxicity; it is a critical event that unleashes Ephexin5-RhoA signaling. When EphB2 levels decline, the tonic inhibition of Ephexin5 is removed, and RhoA becomes hyperactivated. Hyperactive RhoA drives the structural collapse of dendritic spines through multiple convergent mechanisms: it inhibits actin polymerization necessary for spine expansion and stability, activates myosin-mediated actin contraction, and triggers the phosphorylation of cofilin—a protein that severs actin filaments. The consequences of unrestrained RhoA-mediated spine collapse are devastating. Dendritic spines shrink and are progressively eliminated. The structural synaptic losses that correlate most robustly with cognitive decline in Alzheimer's disease thus emerge directly from the pathological reactivation of developmental pruning mechanisms. Importantly, this spine loss occurs through a developmental program whose normal function is essential and beneficial—the problem arises from its inappropriate reactivation in temporal and spatial contexts where it is pathogenic. This insight distinguishes Margolis's model from simpler "toxin accumulation" frameworks: the mechanisms of synaptic destruction in AD are not novel pathological inventions but rather ancient developmental programs operating in inappropriate contexts. Recent research has revealed that Ephexin5 is itself subject to biphasic regulation. In addition to its canonical role activating RhoA, Ephexin5 also regulates Cdc42, another small GTPase that promotes actin polymerization and dendritic spine growth. The dual regulation of RhoA (spine collapse) and Cdc42 (spine growth) by a single protein creates a molecular switch whose state is determined by cellular context. This regulatory switch represents a pleiotropic challenge for therapeutic targeting: simply inhibiting Ephexin5 would simultaneously prevent both pathological spine collapse (via RhoA inhibition) and physiological spine growth (via Cdc42 inhibition). This Cdc42 dual regulation paradox illustrates why translational pathways involving pleiotrophic proteins present exceptional complexity for drug development—interventions must achieve exquisite selectivity to rescue pathological phenotypes without disrupting essential physiological functions. The historiographical table of Alzheimer's disease conceptualization illuminates how Margolis's contributions reframe the disease. Prior to 1991, AD was understood primarily through the lens of pathological anatomy: plaques and tangles were presumed to be the direct cause of neuronal dysfunction. From 1991 onward, the synaptic slaughter paradigm emerged from Robert Terry's landmark correlative studies, establishing that synapse density correlates vastly more robustly with cognitive decline than plaque density. From 1992 onward, the Amyloid Cascade Hypothesis dominated, positing that amyloid-beta initiates a linear cascade culminating in synapse loss. Margolis's contribution reconceptualizes this linearity: rather than amyloid causing synapse loss through direct toxicity, amyloid causes synapse loss by triggering the reactivation of developmental elimination programs. From 2011 onward, the field recognized that soluble amyloid- beta oligomers, rather than fibrillar plaques, mediate the primary neurotoxic effects. Margolis positioned EphB2 depletion and Ephexin5 reactivation as the specific mechanistic consequence of oligomer engagement with synaptic receptors. The second major pillar of Margolis's research program involves the Neuronal Membrane Proteasome (NMP), a radically

novel proteostatic mechanism recently discovered in his laboratory. The NMP is an uncapped, ubiquitin-independent 20S proteasome complex that localizes to the neuronal cell surface and plasma membrane. Unlike the canonical 26S proteasome, which is located primarily in the cytoplasm and nucleus and degrades ubiquitinated substrates, the NMP operates without ubiquitin tagging and preferentially targets activity-induced nascent proteins synthesized at the membrane. The physiological function of the NMP appears to be the rapid, regulated degradation of newly synthesized synaptic proteins, thereby modulating the strength and plasticity of synaptic transmission. Critically, the NMP provides a direct, ApoE4-dependent mechanistic link between the primary genetic risk factor for late-onset Alzheimer's disease and the pathological aggregation of tau—independent of amyloid-beta involvement. ApoE4, unlike the less risky ApoE2 or ApoE3 isoforms, triggers excessive uncapping of 20S proteasomes and their aberrant activation at the neuronal membrane. This uncapped NMP hyperactivation results in pathological, non-selective degradation of activity-induced proteins, including those involved in synaptic stability, cytoskeletal maintenance, and proteostatic regulation. Under conditions of ApoE4-mediated NMP hyperactivation, tau molecules fail to undergo proper conformational folding and instead begin to accumulate in pathological hyperphosphorylated forms. The NMP hyperactivation simultaneously depletes neuroprotective and pro-plasticity proteins, exacerbating proteostatic collapse. This mechanism is particularly significant because it demonstrates that tauopathy can arise through a completely distinct biochemical pathway from the amyloid cascade. An individual carrying the ApoE4 allele could develop tauopathy and cognitive decline through NMP-mediated proteostatic collapse with minimal amyloid pathology. Conversely, an individual with high amyloid burden but favorable ApoE genotype might maintain tauostasis through normal NMP function. This independence of tau aggregation from amyloid pathology explains the epidemiological observation that amyloid burden and tau burden are incompletely correlated across populations and that anti-amyloid therapeutics frequently fail to halt tau spreading. The identification of ARHGEF15 pleiotropy represents a particularly challenging aspect of Margolis's framework. ARHGEF15 is not a simple spine collapse gene; it functions in multiple cellular contexts and regulates multiple downstream effectors. This pleiotropy creates what might be termed "translational barriers" for drug development. Selective inhibition of ARHGEF15 might prevent pathological spine collapse while simultaneously disrupting normal developmental synapse refinement in developing brains or impeding adaptive structural plasticity in healthy neurons. The therapeutic challenge is thus not merely to identify the molecular culprit— Margolis has accomplished this—but to devise interventions sufficiently selective to rescue pathological phenotypes without disrupting essential physiological functions. This represents a profound technical and conceptual challenge distinct from the earlier protein-ablation paradigm. The convergence of Margolis's Ephexin5 pathway with the broader excitatory insufficiency framework proposed by Moosmann and Rappoport is conceptually elegant. Excitatory insufficiency creates a cellular environment of energetic and trophic deprivation. Under such conditions, the brain's developmental programs for synaptic pruning become increasingly permissive—the system essentially responds to trophic insufficiency by eliminating synapses. The reactivation of

Ephexin5-RhoA signaling thus emerges not merely as an amyloid-driven phenomenon but as a deeper consequence of the excitatory deficit that triggers amyloid upregulation. The NMP hyperactivation under ApoE4 conditions simultaneously creates a proteostatic crisis that prevents proper tau metabolism. These multiple pathways converge on a single phenotype—synaptic attrition and proteostatic collapse—through distinct but complementary molecular mechanisms. --- Figure 6.1: ApoE4 Impairs Neuronal Membrane Proteasome Localization, Driving Tau Aggregation. The NMP (20S complex at the plasma membrane) degrades newly synthesized proteins to maintain proteostasis. ApoE4 selectively reduces NMP membrane localization, causing nascent tau to misfold and form sarkosyl-insoluble aggregates.

7. Competitive Synaptic Plasticity and Monomer

Depletion: The Huang Paradigm The previous chapters established that amyloid-beta and phosphorylated tau, rather than being primary toxins, function as compensatory responses to upstream structural and functional deficits. Yet this framework invites a critical mechanistic question: what is the precise physiological function of amyloid-beta itself in the healthy brain, and how does its compensatory upregulation paradoxically accelerate pathology? Zhen Huang's Competitive Synaptic Plasticity Hypothesis provides the answer through a paradigm- shifting reconceptualization of amyloid-beta as a biphasic, concentration- dependent neuromodulator derived from ancient antimicrobial immunity mechanisms. At physiological, monomeric concentrations, amyloid-beta suppresses microglial inflammatory pathways and facilitates competitive synaptic plasticity. At pathological, oligomeric concentrations, amyloid-beta becomes a "punishment" signal triggering synaptic elimination. The critical innovation of Huang's framework is the Monomer Depletion Hypothesis: the disease mechanism is not amyloid toxicity but rather the loss of protective soluble monomers through aggregation, thereby removing the physiological brake on microglial activation. Amyloid-beta exists across an evolutionary phylogeny as an ancient, highly conserved peptide that shares remarkable structural and functional homology with bacterial antimicrobial peptides (AMPs). Like classical AMPs, amyloid-beta possesses amphipathic character, can form oligomeric structures capable of disrupting microbial membranes, and exhibits direct antimicrobial activity against numerous pathogens including Herpes Simplex Virus and various bacteria. This evolutionary conservation suggests that amyloid-beta's role in the healthy brain is not a modern accident of neural evolution but a deeply ancient function preserved through millions of years of mammalian and vertebrate development. The Competitive Synaptic Plasticity Hypothesis proposes that this ancient antimicrobial function has been co-opted for a distinct purpose in the mammalian central nervous system: the regulation of intraspecies synaptic competition. The biphasic action of amyloid-beta defines the framework. At low, physiological concentrations—in the picomolar to low nanomolar range— monomeric amyloid-beta exhibits profound neuroprotective and neurotrophic properties. It enhances NMDA receptor-dependent long-term potentiation, increases the probability of neurotransmitter release at hippocampal synapses, facilitates

neuronal growth and survival, and reduces oxidative stress. These low-concentration effects are mediated through a recently elucidated signaling cascade involving the Amyloid Precursor Protein (APP) itself, the heterotrimeric G-protein activator Ric8a, and downstream G-protein signaling pathways. The APP-Ric8a cascade functions as a microglial suppression mechanism: monomeric amyloid-beta activates this pathway to maintain microglia in a surveilling, non-inflammatory state. This function is critical for the health of the neural microenvironment—active, inflammatory microglia directly damage synapses and promote neuronal apoptosis. At high, pathological concentrations—in the micromolar range typical of brain tissue from advanced Alzheimer's patients—amyloid-beta oligomerizes and exhibits a completely opposite effect. Oligomeric amyloid-beta binds to neuronal receptors including EphB2 (as described in Margolis's framework), triggers synaptic pruning via complement activation and the C4d-LilrB2 axis (as detailed in the Shatz-Brott framework), and activates microglia to produce pro-inflammatory cytokines and engage in destructive engulfment of synapses. This biphasic action—neuroprotective at low concentrations, neurotoxic at high concentrations—is not unique to amyloid-beta; many signaling molecules exhibit concentration-dependent biophysical switching. The critical insight is that this biophysical property is fundamental to the molecule's function. The Flower protein fitness checkpoint system represents a crucial mechanistic component of synaptic competition in the healthy brain. Flower proteins sense the activity-dependent integrity and metabolic health of synapses. Weakly active, metabolically compromised synapses trigger Flower-mediated pruning mechanisms. Strongly active, metabolically robust synapses are protected. In the healthy brain, amyloid-beta-driven Flower checkpoint activation ensures that only metabolically viable, activity- supported synapses are retained. This is developmental synapse refinement extended into adulthood. However, when amyloid-beta oligomerizes to pathological concentrations, Flower checkpoints become indiscriminately activated, leading to excessive pruning and synaptic loss even from metabolically normal neurons. The Monomer Depletion Hypothesis represents the conceptual core of Huang's framework and explains the paradoxical acceleration of neurodegeneration by amyloid-beta itself. As amyloid-beta production increases in response to excitatory insufficiency (the upstream driver identified by Moosmann and Rappoport), the newly synthesized monomers face a thermodynamic choice: they can either remain soluble as monomers or aggregate into oligomers and plaques. The aggregation process is governed by kinetic and thermodynamic parameters influenced by pH, ionic strength, proteolytic processing, and the presence of seeding structures (pre-existing plaques and oligomers). As amyloid-beta levels rise, a progressively larger fraction undergoes aggregation. This aggregation creates what Huang terms a "thermodynamic sink"—a depot of aggregated amyloid-beta that acts like a chemical precipitation reaction, drawing dissolved monomers from solution into the solid phase. The critical consequence is that increased total brain amyloid paradoxically causes a decrease in soluble monomer concentrations. This counterintuitive relationship emerges from basic thermodynamics: if total amyloid increases while aggregation efficiency remains constant, the absolute amount of monomer may remain constant or decrease relative to the total pool. The brain responding to excitatory insufficiency by upregulating amyloid-beta production thus

inadvertently depletes the very monomer pool essential for maintaining microglial suppression and synaptic stability. This monomer depletion removes the physiological brake on microglial activation. Microglia, no longer suppressed by low-concentration amyloid-beta signaling, become activated. Activated microglia upregulate pro- inflammatory cytokines including IL-1beta, IL-6, and TNF-alpha. These cytokines trigger complement cascade activation and recruit matrix metalloproteinase-9 (MMP9) hyperactivation, culminating in massive, indiscriminate synaptic loss. The normal versus pathological pruning table provides essential context. In normal synaptic pruning during development and learning, individual weakly active synapses are selectively eliminated based on activity- dependent and metabolic criteria. Pruning is spatially restricted to specific connections and temporally regulated through developmental epochs. In pathological pruning under Alzheimer's disease conditions, synaptic elimination becomes excessive, non-selective, and temporally dysregulated. Synapses that should be retained are eliminated. The neuronal circuits that underlie cognition are progressively dismantled. What was an elegant refinement mechanism becomes a catastrophic elimination program. The paradigm shift table chronicling the historical evolution of amyloid understanding illuminates the radical nature of Huang's contribution. Prior to the 1980s, amyloid-beta was not identified as a distinct molecular species. From 1980 to 1990, amyloid-beta was characterized as the principal constituent of senile plaques. From 1990 to 2015, the amyloid cascade hypothesis dominated, positing that Aβ accumulation initiates a linear pathological cascade. From 2015 to 2022, the field recognized that soluble oligomers, rather than fibrillar plaques, mediate primary neurotoxicity. Huang's contribution, emerging from 2022 onward, reconceptualizes amyloid-beta's physiological role entirely: it is not a toxin or a pathological byproduct, but a neuropeptide-like signaling molecule whose normal, low-concentration function is essential for brain health. The disease emerges not from amyloid toxicity but from the loss of monomer-mediated neuroprotection as aggregation creates a thermodynamic sink. This framework makes a striking and seemingly paradoxical prediction: anti-amyloid therapies, by accelerating the clearance of existing amyloid— both monomers and aggregates—would further deplete soluble monomer concentrations in the short term, potentially worsening the monomer depletion state. Some clinical data support this prediction: certain anti- amyloid monoclonal antibodies have been observed to accelerate cognitive decline in certain patient populations. If the monomer depletion hypothesis is correct, rational therapeutics would focus not on global amyloid clearance but on preventing aggregation while maintaining monomer bioavailability. Such interventions might include antagonism of amyloid aggregation (without promoting hydrolysis), promotion of monomer bioavailability through APP-Ric8a pathway activation, and simultaneous suppression of the downstream microglial and complement cascades that execute synaptic loss once monomer depletion occurs. The evolutionary conservation of Aβ antimicrobial function extends beyond structural homology to functional principle. Bacteria compete for resources within biofilms and complex microbial communities through the production of antimicrobial peptides that inhibit competitors while leaving kin relatively unharmed. Synapses within the brain, it is hypothesized, compete for trophic resources (neurotrophic factors, energy substrates, synaptic vesicle components) using an analogous

mechanism. Weakly active synapses produce less amyloid-beta; strongly active synapses produce more. The monomeric amyloid-beta from active synapses suppresses the microglial inflammatory response that would otherwise damage neighboring weak synapses. When amyloid-beta aggregates, this competitive mechanism breaks down, and microglia become indiscriminately destructive. The evolutionary conservation of this mechanism from bacterial competition to neuronal competition suggests that it represents a fundamental biochemical principle that evolution has repeatedly leveraged for diverse biological contexts. The intraspecies synaptic competition framework thus unifies the developmental pruning paradigm, the role of activity-dependent mechanisms in learning and memory, and the pathological mechanisms of neurodegeneration. All three phenomena can be understood through the lens of competitive interactions between synapses for trophic support and neural circuit incorporation. In health, this competition is regulated, proportionate, and beneficial. In Alzheimer's disease, the regulation breaks down, and competition becomes destructive overexpression of an ancient pruning program. This is the monomer depletion paradigm—a disease of loss rather than accumulation.

A second 2022 Oskar Fischer Silver Prize framework, the innate-immunity / autoimmune-disorder model of Donald Weaver, reaches the AMP-character of amyloid-beta through a mechanistic logic that should not be conflated with Huang's. Where Huang locates the disease in the loss of protective monomer through an aggregation-driven thermodynamic sink, Weaver locates it in the misdirection of AMP-class Aβ at neuronal substrate whose membrane lipidomics—surface charge, exposed ganglioside head groups, oxidized phospholipid load—have drifted toward biophysical profiles that resemble the bacterial targets the AMP program evolved to discriminate against. On the Weaver framing, pathological Aβ deployment is not a quantitative imbalance of monomer versus aggregate; it is a qualitative recognition error in which the innate immune system identifies self as non-self and deploys an effector that produces pore-formation in neuronal membranes, necrotic rather than apoptotic neuronal death, and release of GM1-Aβ complexes that act as damage-associated molecular patterns propagating the misdirection to surrounding tissue. The two frameworks are complementary rather than competing: Huang explains why the brake on microglial activation fails (monomer depletion through aggregation), Weaver explains why the deployed AMP causes harm (identity error against drifted neuronal membranes), and together they articulate a more complete account of the AMP arm than either supplies alone—the loss of suppression is Huang's contribution; the substrate of attack is Weaver's. The Weaver framework also licenses a distinct therapeutic axis absent from the Huang and Moosmann-Rappoport programs: pharmacological modulation of amino-acid metabolic pathways. Weaver's 2026 *NeuroSci* paper proposes β-alanine as an unexploited target on the grounds that β-alanine modulates both GABAergic and glutamatergic tone, exhibits antioxidant activity, and binds directly to Aβ and tau aggregates; the broader Weaver program identifies tryptophan and arginine metabolism as additional handles. This amino-acid-metabolic therapeutic axis is mechanistically independent of the anti-aggregation, monomer-bioavailability, and excitatory-tone-restoration axes that the prior frameworks license, and its inclusion enlarges the therapeutic surface available to the

synthesis without competing with the existing recommendations.

8. The C4d-LilrB2 Axis: Dual-Pathway Synaptic

Pruning and the Convergence of Immunity and Structure The previous chapters have established that Alzheimer's disease involves the aberrant reactivation of developmental synaptic pruning mechanisms in response to upstream structural and functional perturbations. This chapter evaluates the seminal research by Barbara K. Brott and Carla J. Shatz, which identifies the complement cleavage product C4d and the neuronal receptor Leukocyte immunoglobulin-like receptor subfamily B member 2 (LilrB2, or its murine ortholog PirB) as the final common pathway through which neuroimmune signals are transduced into structural synaptic collapse. This C4d-LilrB2 axis represents a critical convergence point where immunological signaling cascades are integrated with neuronal structural biology, providing a mechanistic bridge between the systemic immune dysregulation of aging and the specific synaptic pathology defining cognitive decline. The historiographical context of this discovery requires acknowledgment of the foundational Stevens-Barres framework established in the late 1990s and early 2000s. C. Jane and Ben Barres' revolutionary research demonstrated that microglia and astrocytes actively participate in the elimination of synapses during development and in pathological contexts. This discovery fundamentally displaced the idea that glia were mere support cells; instead, they emerged as active participants in synaptic architecture. The initial Stevens-Barres model focused on the role of astrocyte-derived complement components (particularly C1q, C3, and their activated fragments) and their interaction with microglial CR3 receptors (complement receptor 3). Microglia, recognizing complement-tagged synapses through CR3, engulfed and eliminated these synaptic structures. Brott and Shatz's contribution fundamentally extends and reconceptualizes this framework. Rather than viewing complement fragments as mere tagging molecules recognized by microglial engulfment machinery, they propose that C4d functions as a high-affinity, physiological ligand for the neuronal receptor LilrB2. This reconceptualization is conceptually profound: C4d is not a "dead-end" fragment recognized passively by immune cells, but an active signaling molecule that directly instructs neurons to execute structural collapse. This shifts the locus of synaptic elimination from purely microglial engulfment to include neuron-autonomous structural collapse programs activated by C4d-LilrB2 signaling. The biochemical evidence for C4d-LilrB2 interaction is rigorous and multifaceted. Initial binding studies demonstrated that C4d binds to LilrB2 with high affinity (Kd in the picomolar to low nanomolar range), substantially higher affinity than other characterized LilrB2 ligands including MHC-I and amyloid-beta. Surface plasmon resonance, co-immunoprecipitation, and mammalian two-hybrid assays all confirmed direct molecular interaction. Critically, C4d binds LilrB2 through epitopes distinct from those recognized by MHC-I, suggesting that C4d represents a primary, high-affinity ligand rather than an alternative

binding partner. This biochemical characterization refutes alternative hypotheses suggesting C4d serves merely as a tagging molecule for microglial clearance; instead, it positions C4d as a dedicated signaling ligand with its own receptor specificity. LilrB2 functions as a multivalent convergence hub for multiple synaptic danger signals. Beyond C4d, LilrB2 binds amyloid-beta (particularly oligomeric forms), MHC-I molecules, and likely other yet-uncharacterized synaptic ligands. This multivalence is significant: synapses experiencing stress from multiple sources (complement activation, oligomeric amyloid- beta accumulation, MHC-I upregulation) deliver amplified signals through LilrB2. The receptor thus functions not as a simple binary switch but as an analog integrator of synaptic damage signals. Synapses with mild or transient insults activate LilrB2 weakly; synapses experiencing severe or sustained damage activate it strongly. This analog integration ensures that only appropriately damaged synapses are eliminated. The downstream intracellular cascade triggered by C4d-LilrB2 receptor engagement involves the cofilin-actin regulatory axis, providing the structural effector mechanism for dendritic spine collapse. LilrB2 activation engages Src-family protein tyrosine kinases, which phosphorylate substrates that regulate the activity of downstream signaling cascades including PAK (p21-activated kinase) and LIMK (LIM kinase). LIMK, in turn, phosphorylates and inactivates cofilin. However, LilrB2 engagement paradoxically also activates signaling pathways that drive dephosphorylation and activation of cofilin. Under conditions of sustained LilrB2 engagement, cofilin undergoes hyperactivation and hyperphosphorylation in a complex temporal pattern. Hyperactivated cofilin severs actin filaments, destabilizing the actin cytoskeleton that forms the structural core of the dendritic spine. This severing unleashes a catastrophic positive feedback: as actin filaments are severed, cofilin cannot be sequestered by F-actin binding, and it remains in the active form. The active cofilin continues to sever additional actin filaments. Cofilin-actin rods—structures composed of stacked, crosslinked actin filaments bound by hyperactive cofilin—accumulate within the spine. These rods represent a structural transition point: they are neither normal actin cytoskeleton nor complete cytoskeletal collapse, but a pathological intermediate state. The accumulation of cofilin-actin rods within dendritic spines drives their retraction and eventual loss. In vivo validation of the C4d-LilrB2 axis emerges from elegant mouse genetics. PirB (the murine ortholog of LilrB2)-knockout mice exhibit resistance to amyloid-beta-induced synaptic loss and cognitive decline in Alzheimer's disease models. Critically, this protection occurs even when amyloid-beta accumulation remains robust. This dissociation between amyloid pathology and synaptic protection demonstrates that synaptic loss is not an inevitable consequence of amyloid accumulation but specifically requires LilrB2/PirB signaling. Conversely, transgenic mice overexpressing PirB in neurons exhibit enhanced susceptibility to synaptic loss in response to amyloid-beta or other damage signals. This bidirectional genetic control strongly supports the causal role of the LilrB2 pathway in synaptic elimination. Spatial validation through high-resolution array tomography provides crucial subcellular localization data. Array tomography involves ultrathin serial sectioning of brain tissue and immunofluorescent staining of consecutive sections, permitting three-dimensional reconstruction of subcellular structures. Using this approach, Brott, Shatz, and colleagues demonstrated that C4d and

LilrB2 are colocalized at the synaptic cleft with approximately sixty percent colocalization frequency at excitatory synapses. This high colocalization frequency is non-random and substantially exceeds what would be predicted by chance distribution of the two molecules within the neuropil. Furthermore, C4d deposition within synapses correlates with nearby cofilin-actin rod formation, providing spatial evidence for the biochemical cascade. The genomic signatures of LilrB2 and related molecules reveal ethnic- specific and population-level risk variation. Genome-wide association studies have identified multiple variants in the LILRB2 locus and related immune genes as risk factors for Alzheimer's disease in specific populations. Remarkably, certain LILRB2 variants exhibit ethnic specificity —they confer significant risk in European ancestry populations but negligible risk in African ancestry populations, or vice versa. This ethnic specificity does not reflect population-level differences in allele frequency alone, but rather indicates genuine biological differences in the genetic contribution to disease risk across populations. This heterogeneity implies that the therapeutic importance of the LilrB2 axis may vary across populations, with significant implications for precision medicine approaches. The C4d-LilrB2 axis also provides insight into the ethnic-specific risk paradox of Alzheimer's disease. African ancestry populations exhibit lower prevalence of late-onset Alzheimer's disease relative to European ancestry populations, despite experiencing comparable exposure to apolipoprotein E4 (ApoE4), which is a dominant genetic risk factor. This paradox has been unexplained within traditional frameworks. However, genetic variation in the complement cascade—particularly in C4, C4A/C4B copy number variation, and downstream complement regulatory genes—shows significant population stratification. African ancestry populations carry genetic variants that may confer reduced complement activation or enhanced complement regulation. Reduced C4d generation through altered C4A/C4B copy numbers could thus explain the lower disease burden in these populations. This example illustrates how the C4d-LilrB2 framework provides biological explanatory power for previously mysterious epidemiological observations. C4d emerges as a highly promising clinical biomarker for Alzheimer's disease. Cerebrospinal fluid (CSF) C4d levels are elevated approximately fourfold in Alzheimer's disease patients relative to healthy controls, with substantial diagnostic discriminatory power. Serum complement activation fragments similarly show elevation, though with more modest effect sizes. The advantage of C4d as a biomarker derives from its mechanistic proximity to synaptic pathology: C4d deposition directly drives synaptic elimination through LilrB2 engagement, making it a more mechanistically relevant measure than distant proxies like total amyloid or phosphorylated tau. Longitudinal biomarker studies indicate that CSF C4d elevation precedes cognitive decline measurably, making it potentially useful for prognosis and disease staging in asymptomatic or mildly symptomatic individuals. Therapeutic antagonism of the LilrB2 pathway represents a conceptually distinct approach from current disease-modifying therapies. Rather than targeting upstream amyloid or tau pathology, anti-LilrB2 strategies aim to block the final common pathway of synaptic elimination. Multiple experimental approaches show promise: monoclonal antibodies that block the C4d-LilrB2 interaction, soluble receptor decoys that sequester C4d, and small-molecule inhibitors of downstream LIMK/cofilin signaling. Remarkably, anti-LilrB2 antibodies or receptor antagonism

protect synapses from elimination even in the presence of robust amyloid pathology, as demonstrated in animal models. This protection occurs through two mechanisms: first, blocking neuronal LilrB2 signaling prevents the C4d- driven cofilin-actin cascade within neurons, preserving spine structure. Second, LilrB2 on microglial surfaces functions as an inhibitory receptor that suppresses microglial activation and TNF-alpha production; blocking this inhibitory signal paradoxically enhances beneficial microglial phagocytosis of plaques and degradation of oligomeric amyloid-beta. This dual nature of LilrB2 signaling—inhibitory on neurons, inhibitory on microglia—creates what might be termed a "therapeutic paradox." Blocking neuronal LilrB2 prevents synaptic suicide; simultaneously blocking microglial LilrB2 inhibition unleashes beneficial phagocytic responses. The intersection with TREM2 (Triggering Receptor Expressed on Myeloid cells 2) signaling is particularly relevant. TREM2 activation promotes microglial survival and phagocytic function; removing the inhibitory signal from LilrB2 permits TREM2 signaling to function optimally. Thus, anti-LilrB2 therapies can simultaneously prevent neuron-autonomous synaptic destruction and enhance microglial clearance of pathological protein aggregates. The C4d-LilrB2 framework also accounts for the role of complement- regulatory proteins in Alzheimer's disease protection. CD55 (decay- accelerating factor), CD46 (membrane cofactor protein), and CD59 (complement restriction protein) all function to limit complement activation and C4d generation. Genetic variants and expression levels of these regulatory proteins show association with Alzheimer's disease risk. Individuals with enhanced complement regulation through higher CD55, CD46, or CD59 expression experience reduced synaptic C4d deposition and correspondingly lower disease risk. This provides a mechanistic understanding of how genetic variation in complement regulation influences disease susceptibility: enhanced regulation reduces C4d-driven synaptic elimination. The Framework Evolution table chronicles the historical progression of understanding regarding synaptic loss mechanisms. Prior to 1991, synaptic loss was attributed to gross neuronal death. From 1991 to 2000, synapse density emerged as the primary correlate of cognitive decline, but the mechanism remained obscure. From 2000 to 2010, the field focused on amyloid-beta oligomer toxicity to synapses. From 2010 to 2015, the role of developmental pruning mechanisms reactivated in adulthood was recognized through Margolis's Ephexin5 work. From 2015 to 2025, multiple converging mechanisms of synaptic elimination were appreciated— Ephexin5-RhoA driven collapse, microglial engulfment, and complement- mediated effects. The Brott-Shatz contribution from 2025 onward provides the direct C4d-LilrB2 mechanistic pathway linking complement cascade activation to synaptic structural collapse in a neuron-autonomous manner. The Cofilin-Actin Regulatory Axis table details the molecular choreography of structural synaptic collapse. At baseline in healthy neurons, cofilin exists in a predominantly phosphorylated, inactive state. Activity-dependent unphosphorylation activates cofilin, permitting actin severing essential for dendritic spine growth and synaptic plasticity. LilrB2-mediated signaling under pathological conditions drives excessive cofilin activation exceeding normal plasticity ranges. Hyperactivated cofilin severs actin filaments indiscriminately, overwhelming the capacity of actin-nucleating factors to regenerate filaments. The balance tips toward net actin disassembly. Cofilin-actin rods

accumulate, representing a pathological cross-linked state. The dendritic spine, whose structure depends upon dynamic actin polymerization, progressively retracts and is ultimately eliminated. This comprehensive evaluation of the C4d-LilrB2 axis establishes it not as an isolated mechanism but as the convergence point of multiple upstream pathological processes identified in previous chapters. Moosmann's excitatory insufficiency triggers compensatory amyloid-beta upregulation. Rappoport's lipid raft degradation impairs NMDA receptor trafficking. Margolis's Ephexin5-RhoA pathway reactivates developmental pruning. Huang's monomer depletion permits microglial activation. All of these upstream processes ultimately converge on the complement cascade, generating C4d that engages neuronal LilrB2, triggering the cofilin-actin cascade and synaptic structural collapse. The C4d-LilrB2 axis thus represents the final common pathway through which diverse upstream pathologies are translated into the specific synaptic pathology—synaptic loss—that fundamentally defines cognitive decline in Alzheimer's disease. Therapeutically targeting this axis offers potential to prevent synaptic elimination even in individuals with established upstream pathologies, thereby potentially interrupting or arresting disease progression regardless of the specific upstream cause. --- Summary These four chapters form an integrated synthesis of contemporary Alzheimer's disease research, tracing the pathological cascade from structural membrane degradation (Rappoport) through functional excitatory insufficiency (Moosmann), through the reactivation of developmental pruning programs (Margolis), through biphasic amyloid signaling (Huang), to the final synaptic structural collapse via the complement cascade (Shatz-Brott). The synthesis reconceptualizes Alzheimer's disease from a primary proteinopathy to a cascade of progressively amplifying systems failures driven by upstream structural and functional perturbations. This framework positions amyloid-beta and phosphorylated tau as physiological compensatory responses to fundamental deficits rather than disease- causing toxins, with profound implications for therapeutic strategy. The work collectively demonstrates why therapeutic strategies based on protein ablation have repeatedly failed and suggests that future interventions must target the upstream structural and functional deficits while simultaneously blocking the downstream pathological cascades of synaptic elimination. Figure 8.1: The Dual-Pathway Model of Complement-Mediated Synapse Pruning. C4b activates C3, leading to microglial engulfment via CR3; simultaneously, the C4d fragment binds neuronal LilrB2, triggering cofilin-actin rod formation and autonomous dendritic spine shrinkage. Figure 8.2: PirB Deletion Prevents C4d-Induced Dendritic Spine Loss. In vivo C4d infusion significantly reduces spine density in wild-type mice but has no effect in PirB knockout mice, demonstrating that the PirB receptor is strictly required for C4d-mediated synaptic elimination. PART III Cross-Framework Network Synthesis Chapters 9–15

9. The Endosomal Nexus

The endosomal system emerges from close examination of multiple frameworks as the singular anatomical and biochemical nexus where the ostensibly divergent pathogenic mechanisms of Alzheimer's disease converge. Four frameworks—Ramsden's lipid peroxidation model, Small's retromer hypothesis, Gouras's inside-out paradigm, and partially Huang's competitive plasticity framework—converge on the early endosome as the critical locus of disease initiation and amplification. This chapter maps the molecular interface where lipid peroxidation disrupts receptor trafficking, retromer dysfunction jams endosomal recycling, intraneuronal amyloid-beta accumulates in multivesicular bodies, and APP processing dysregulation traps proteolytic fragments in compartments of prolonged transit time. Understanding this nexus is essential to conceptualizing how multiple upstream insults funnel into a single anatomical compartment where they amplify each other's pathogenic effects. The Ramsden framework establishes the initial perturbation. Within the endosomal microenvironment, ApoE molecules carrying polyunsaturated fatty acid (PUFA) cargo undergo severe oxidative damage if they lack the protective intermolecular disulfide bridge characteristic of APOE2 and APOE3. The APOE4 allele, in contrast, cannot form these protective bonds due to amino acid substitutions at positions 112 and 158. This structural vulnerability renders the PUFA cargo—cholesterol, ethanolamine phosphoglycerides, and docosahexaenoic acid—uniquely susceptible to peroxidation. The resulting reactive lipid aldehydes (4-hydroxynonenal, malondialdehyde, and related species) do not merely damage membrane structure in situ. Rather, these aldehydes undergo Schiff base formation and Michael addition reactions with lysine and cysteine residues on the ApoE protein itself and, critically, on its cognate receptor ApoER2. The consequence is the formation of covalent crosslinks that trap ApoER2 in the early endosome. This trapment is not a passive sequestration. Instead, it represents the catastrophic disruption of a critical synaptic signaling pathway. The ApoER2-Reelin-Dab1 cascade normally drives both postsynaptic structural plasticity and metabolic homeostasis. Reelin, secreted from GABAergic interneurons, binds ApoER2 and its co-receptor LDL receptor-related protein 8 (LRP8) to initiate rapid phosphorylation of Dab1, which in turn suppresses glycogen synthase kinase 3 beta (GSK3β) via Src-family kinase signaling. When ApoER2 is sequestered and crosslinked in the endosome by oxidized ApoE, Reelin signaling becomes impossible. Dab1 accumulates in its unphosphorylated state. GSK3β escapes inhibition and becomes constitutively hyperactive. This hyperactivation cascades through two distinct effectors: first, through the LIMK1-cofilin axis, which regulates actin filament dynamics; and second, through the direct phosphorylation of tau protein on residues that accumulate in neurofibrillary tangles. The Small framework, focused on retromer dysfunction, identifies a second endosomal vulnerability that intersects precisely at the early endosomal compartment. The retromer complex—composed of the VPS26 (variant a or b), VPS29, and VPS35 proteins—mediates the retrieval of cargo proteins from the early endosome back to the trans-Golgi network. When retromer assembly is disrupted through VPS35 mutations, VPS26b loss-of-function variants, or through the dysmotility cascade that compromises SORL1 trafficking, the early endosome becomes a trafficking jam. APP and BACE1 are both retrieved from early endosomes via SORL1-mediated retromer- dependent transport. When this retrieval fails, both

APP and BACE1 experience prolonged residence time within the early endosomal compartment. This extended co-localization dramatically increases the probability of proteolytic cleavage of APP by BACE1, generating the C- terminal fragment 99 (βCTF). The βCTF itself becomes part of the jam—it cannot be efficiently retrieved or degraded, and it accumulates within the early endosome. The Small framework identifies a molecular cascade downstream of retromer dysfunction that is particularly significant. The lipid environment of the endosome changes when trafficking is perturbed. Lipid rafts— cholesterol-rich, sphingolipid-enriched microdomains—become concentrated within endosomal compartments when proper trafficking flow is interrupted. SORL1, a retromer-dependent transporter, preferentially binds APP in lipid raft environments and facilitates its anterograde movement. When SORL1 function is compromised, not only does APP residence time increase, but the lipid raft composition of the endosome itself is altered. This creates a second-order perturbation: the biophysical environment of the endosome becomes increasingly organized toward accumulation of amyloidogenic proteolytic products. A third molecular player at the endosomal nexus is the vacuolar ATPase (v- ATPase) complex, which maintains the acidic pH essential for both endosomal function and the catalytic activity of proteases including BACE1. The Ramsden framework emphasizes that the accumulation of oxidized lipids—particularly docosahexaenoic acid peroxides—within endosomal membranes impairs v-ATPase assembly and function. The v-ATPase is an extremely complex multi-subunit proton pump; its assembly and activity are exquisitely sensitive to lipid composition. Peroxidized PUFAs integrate into the lipid bilayer and disrupt the conformational dynamics necessary for proton translocation. As v-ATPase function declines, endosomal pH rises. This rise in pH paradoxically makes the endosomal environment simultaneously more and less permissive for disease-driving processes: BACE1 activity decreases (as it has an acidic pH optimum), but this decreased activity is coupled with increased residence time of substrate, compensatory upregulation of BACE1 expression, and accumulation of intermediates. Moreover, a rising pH in the early endosome signals calcium dysregulation through mechanisms involving the ryanodine receptor and two-pore-domain calcium channels present on the endosomal membrane, leading to secondary mitochondrial calcium overload. The Gouras framework contributes a critical temporal and anatomical specification to the endosomal nexus. Within the synaptic terminal, synaptic vesicles recycle through the early endosome and, under physiological conditions, a fraction of the early endosomal volume gets incorporated into multivesicular bodies (MVBs) destined for lysosomal degradation. Gouras's essential observation is that amyloid-beta 42, the 42-amino-acid variant of Aβ, accumulates specifically within MVBs at synaptic terminals. This intraneuronal Aβ42 is not the product of extracellular plaque formation; rather, it is generated from APP processing within the endosomal compartment itself, then sequestered in MVBs. The architecture of MVBs is determined by the ESCRT (endosomal sorting complex required for transport) machinery, which recruits ubiquitinated cargo proteins into the internal vesicles of the MVB. Aβ42, being highly lipophilic and amyloidogenic, aggregates within these internal vesicles and becomes stabilized there. Critically, Aβ42 within MVBs is sequestered from the cytosol and from the degradative machinery of the cell. Gouras emphasizes that

intraneuronal Aβ42 accumulation precedes the appearance of extracellular plaques by 10 to 15 years in the Braak staging system, and this early intraneuronal phase is when the maximal synaptic toxicity occurs. The mechanism of this toxicity is proposed to involve both the direct effects of oligomeric Aβ42 on the MVB membrane and the secondary consequences of impaired lysosomal degradation. If the MVB is unable to fuse with lysosomes—either because of disrupted endosomal-lysosomal traffic or because of continued ESCRT-mediated sequestration of cargo—then the synaptic terminal experiences an accumulation of Aβ42 within the MVB in addition to unresolved membrane damage, lipid peroxides, and mitochondrial dysfunction. A particularly elegant convergence point emerges when the Huang framework is considered alongside the endosomal-centric views. Huang proposes that Aβ monomer, under normal conditions, serves a synaptic function—possibly modulating NMDA receptor trafficking, facilitating long- term potentiation, or supporting dendritic spine stability. When Aβ monomer becomes depleted due to sequestration in endosomal and MVB compartments (either through aggregation in situ or through lysosomal degradation), the synapse loses this trophic function. This monomer depletion hypothesis is not merely a redescription of the aggregation problem; it identifies a gain of pathological function through loss of a normal physiological signal. From the endosomal nexus perspective, the depletion of normal synaptic Aβ monomer is a direct consequence of excessive endosomal generation and sequestration of Aβ42. A further convergence emerges at the intersection of endosomal dysfunction and protease dysregulation, in the form of a shift in the proteolytic environment of the endosomal lumen itself. When retromer dysfunction traps βCTF in the endosome, the fragment becomes a substrate not only for additional proteolysis by presenilin-containing γ-secretase but also for less-specific proteases. The identity of the individual enzymes acting on Aβ species under these conditions remains incompletely defined, but the principle is well-established: the endosomal compartment is rich in proteases with varying specificities, and when substrate residence time increases, the proteolytic landscape within the endosome shifts from typical APP processing toward more promiscuous and potentially more toxic cleavage patterns. The endosomal lipid environment itself undergoes profound remodeling when the integrated perturbations of Ramsden's lipid peroxidation, Small's retromer dysfunction, and Gouras's intraneuronal Aβ accumulation converge. The incorporation of peroxidized PUFAs into endosomal membranes alters the biophysical properties of the membrane, changing its curvature, deformability, and capacity to generate the precise membrane invaginations necessary for MVB formation and ESCRT-mediated cargo sorting. Simultaneously, the accumulation of Aβ oligomers within MVBs affects membrane tension and can lead to membrane rupture or incomplete MVB biogenesis. The lipid raft architecture becomes increasingly enriched in oxidized lipids, which have different packing properties than unperoxidized lipids. This lipid raft reorganization has multiple consequences: it alters the localization of signaling proteins, it affects the activation state of kinases like Src family kinases and focal adhesion kinase, and it influences the trafficking of additional cargo molecules. The calcium dynamics within the endosomal system also become profoundly dysregulated when these four frameworks converge at the endosomal nexus. Ramsden's framework identifies oxidative damage to

the ryanodine receptor and related calcium release channels. Small's framework notes that retromer dysfunction results in accumulation of calcium-regulating proteins in the early endosome, as these proteins normally depend on retrograde trafficking to the ER. Gouras emphasizes that synaptic terminals have exceptionally high rates of calcium turnover, and the accumulation of Aβ42 in endosomal-MVB compartments directly perturbs calcium sequestration. The consequence is a progressive elevation of resting cytosolic calcium in affected neurons, which in turn activates calcium- dependent proteases (calpains), affects mitochondrial function, and triggers apoptotic pathways. The convergence of these mechanisms at the endosomal nexus suggests that the early endosome is not simply a passive compartment where degraded material accumulates. Rather, it becomes a dynamic pathogenic hub where lipid peroxidation creates the oxidative stress that initiates disease, where retromer dysfunction creates the traffic jam that amplifies APP processing, where Aβ42 accumulation in MVBs traps the cell's attempt at proteolytic resolution, and where the resulting lipid and calcium dysregulation propagate secondary pathogenic cascades. This endosomal nexus hypothesis predicts that therapeutic interventions targeting any single point on the endosomal cascade would likely fail unless coordinated with interventions at other points. Conversely, it suggests that restoration of endosomal homeostasis—through enhancement of v-ATPase function, restoration of retromer assembly, reduction of PUFA peroxidation, or improvement of lysosomal fusion and degradation capacity—could simultaneously address multiple mechanistic arms of the disease. Table 1: Endosomal Nexus Convergence Map

Framework Primary Endosomal

Contribution Key Molecular Players Pathological Consequence Ramsden Lipid peroxidation of PUFA cargo; ApoE- ApoER2 crosslinking Peroxidized ApoE, ApoER2, 4-HNE, MDA, GSK3β, LIMK1, cofilin Receptor trapment in endosome; disruption of Reelin signaling; actin dysregulation; tau hyperphosphorylation Small Retromer dysfunction; endosomal traffic jam VPS35, VPS26b, SORL1, APP, BACE1, βCTF, lipid rafts Prolonged APP-BACE1 contact; excessive Aβ generation; altered lipid raft organization; impaired protein retrieval Gouras Intraneuronal Aβ42 accumulation in MVBs ESCRT machinery, γ- secretase, MVB biogenesis factors, Aβ42 oligomers Synaptic endosomal Aβ42 sequestration; toxicity preceding extracellular plaques; impaired lysosomal fusion; synaptic dysfunction Huang Aβ monomer depletion; APP processing dysregulation Aβ monomer, NMDA receptors, synaptic adhesion molecules, APP C-terminal fragments Loss of normal synaptic Aβ function; gain of toxicity through monomer depletion; competitive plasticity failure The endosomal nexus framework resolves several longstanding paradoxes in Alzheimer's disease pathology. First, it explains why intraneuronal Aβ accumulates before extracellular plaques without requiring the full amyloid cascade hypothesis—the intraneuronal accumulation is an inevitable consequence of endosomal-MVB dysfunction, not a prerequisite for or precursor to extracellular plaque formation. Second, it clarifies why both lipid peroxidation and retromer dysfunction are independently pathogenic: they attack the endosomal system from different angles and amplify each other's effects. Third, it provides a mechanistic account for the extreme difficulty in clearing amyloid

from affected brains—Aβ42 sequestered within MVBs is anatomically segregated from both extracellular antibodies and from the cell's own proteolytic and degradative machinery. Fourth, it explains the failure of anti-amyloid therapies; these therapies target extracellular Aβ but leave the endosomal architecture fundamentally intact, allowing continued intraneuronal generation and pathological processing. Finally, it suggests that the "beginning" of Alzheimer's disease is not a molecular event but a compartmental event—the early endosome becomes the locus of disease through the convergence of multiple upstream insults, and understanding disease progression requires understanding how endosomal dysfunction propagates to affect dendritic spine stability, synaptic transmission, and eventually neuronal survival. ---

10. The Compensatory Paradigm

One of the most consequential shifts in contemporary Alzheimer's disease pathogenesis research is the reconceptualization of amyloid-beta and tau from neurotoxic aggregates to compensatory, initially protective responses to a primary pathogenic insult. Four frameworks—Moosmann's chronic excitatory insufficiency hypothesis, Rappoport's allostatic load model, Ramsden's lipid peroxidation framework with its emphasis on Aβ as an antioxidant response, and Huang's monomer depletion hypothesis— independently arrive at the conclusion that Aβ and tau serve protective or functional roles under conditions of cellular stress, and that the pathology of Alzheimer's disease begins not with their production but with the adaptive-to-maladaptive transition. This paradigm shift has profound implications for therapeutic strategy and for understanding why decades of anti-amyloid interventions have failed to halt disease progression. The Moosmann framework provides the most articulate exposition of the compensatory paradigm. Moosmann argues that the primary pathogenic insult in Alzheimer's disease is not the presence of amyloid-beta but the chronic insufficiency of excitatory, glutamatergic neurotransmission at the synaptic level. Specifically, NMDA receptors, which mediate slow, voltage- dependent calcium influx that supports memory consolidation and structural plasticity, become functionally hypoactive. This hypoactivity can arise from multiple upstream causes: loss of dendritic spines (a structural change), decreased glutamate release (a presynaptic change), or altered NMDA receptor trafficking or membrane composition (a postsynaptic change). Regardless of the upstream cause, the postsynaptic cell interprets chronic NMDA hypofunction as a threat to its survival. The cell responds by upregulating production of amyloid-beta. The mechanism through which NMDA hypofunction triggers Aβ upregulation is not arbitrary or incidental. Rather, amyloid-beta serves a specific compensatory function. Under conditions of excitatory insufficiency, Aβ oligomers interact with NMDA receptors and modulate their trafficking and activity. At low concentrations and under physiological conditions, Aβ oligomers can increase NMDA receptor surface expression and synaptic localization through interactions with the receptor's extracellular domain. This represents a genuine compensatory response: the neuron attempts to restore excitatory tone by increasing the number of functional

NMDA receptors available to receive glutamatergic input. Simultaneously, Aβ at low concentrations acts as an antioxidant, scavenging reactive oxygen species generated by mitochondrial stress. If the chronic excitatory insufficiency persists over years to decades, however, the compensatory response becomes maladaptive. The production of Aβ continues, and the oligomers accumulate. At higher concentrations, the same Aβ oligomers that were initially protective become neurotoxic—they hyperactivate NMDA receptors, drive calcium overload, and propagate oxidative stress rather than ameliorating it. The Moosmann framework specifies the molecular mechanisms that govern the transition from compensatory to pathological Aβ production. The regulation of BACE1 expression and localization is responsive to changes in NMDA receptor signaling through cAMP-response element binding protein (CREB) and to changes in neuronal activity through calcium-calmodulin- dependent kinase IV (CaMKIV). During periods of low NMDA signaling, CREB activity decreases, and BACE1 expression is upregulated. This upregulation is not dysregulation but rather a coordinated compensatory response. However, if the stimulus for compensatory Aβ production persists (that is, if the excitatory insufficiency is never resolved), then BACE1 upregulation becomes chronic and maladaptive. Additionally, the chronically elevated neuronal calcium that results from NMDA receptor hypofunction activates calpain proteases, which cleave and dysregulate additional signaling proteins, perpetuating the pathogenic cascade. Rappoport's allostatic load model extends and contextualizes the Moosmann framework through a broader systems biology perspective. Allostatic load is a concept from physiology that describes the cumulative burden of chronic stress on an organism. In Rappoport's framework, Alzheimer's disease results from the allostatic load imposed on the brain by multiple simultaneous homeostatic challenges. These challenges might include chronic mild metabolic stress, intermittent hypoxia, oxidative stress from peripheral sources, or social and psychological stress that is translated into brain chemistry through the neuroendocrine system. In response to this cumulative allostatic load, the brain mounts a coordinated, adaptive response. Tau undergoes hyperphosphorylation as part of a microtubule- stabilization response to metabolic challenge. Aβ is produced and accumulates as an antioxidant and as a modulator of synaptic transmission. Neuroinflammation is triggered as a metabolic stress response that attempts to clear dysfunctional cellular components and restore homeostasis. Rappoport's key insight is the identification of the adaptive-to-maladaptive transition point. The same molecular changes that are initially adaptive—hyperphosphorylated tau stabilizing microtubules, Aβ oligomers protecting against oxidative stress, microglial activation clearing synaptic debris— become pathological when they persist beyond the period of acute stress. If the allostatic challenge is resolved, the adaptive response resolves as well. However, in many individuals, particularly those carrying APOE4, the allostatic challenge becomes chronic. The adaptive response does not deactivate but instead becomes locked in a pathological state. Tau phosphorylation that was initially protective becomes excessive, leading to filament polymerization and neurofibrillary tangle formation. Aβ accumulation that was initially protective becomes toxic through mechanisms of oligomer propagation and prion-like spreading. Microglial activation that was initially neuroprotective becomes neurotoxic, shifting from a pro-healing to a

pro-inflammatory phenotype. The lipid raft hypothesis, particularly as articulated by Rappoport, identifies a specific molecular mechanism for how the adaptive response becomes maladaptive. Lipid rafts are specialized membrane microdomains enriched in cholesterol and sphingolipids. They serve as platforms for the organization of signaling proteins and for the regulation of membrane trafficking. Under conditions of metabolic stress and elevated allostatic load, the lipid raft composition of neuronal membranes changes. APOE4, which differs from APOE3 and APOE2 in its lipid-binding properties and its capacity to facilitate proper lipid raft organization, creates a lipid raft environment that is inherently more reactive to oxidative stress. The lipid rafts enriched in APOE4-bound lipids are more densely packed with cholesterol and are more prone to oxidative damage. This creates a self- reinforcing cycle: oxidative stress drives lipid raft reorganization, which facilitates further oxidative stress. Critically, the lipid raft composition directly affects the trafficking and activity of NMDA receptors. APOE4-influenced lipid raft reorganization leads to altered NMDA receptor localization, reduced synaptic efficacy, and the compensatory Aβ upregulation described by Moosmann. Thus, Rappoport's allostatic load model and lipid raft hypothesis provide a mechanistic bridge between Moosmann's excitatory insufficiency hypothesis and the broader context of APOE4-associated vulnerability. Ramsden's lipid peroxidation framework contributes a crucial insight to the compensatory paradigm: amyloid-beta itself, in its monomeric and early oligomeric forms, serves an antioxidant function. This is not speculative; it has been experimentally demonstrated that Aβ monomer and dimer can efficiently scavenge reactive oxygen species, including the highly reactive hydroxyl radical and superoxide anion. The antioxidant activity is mediated through the tyrosine residue at position 10 of the Aβ sequence, which can participate in electron transfer reactions and can form tyrosyl radicals that are less reactive than the original ROS species. From the Ramsden perspective, when polyunsaturated fatty acids undergo peroxidation—driven by either extrinsic sources (diet, environmental toxins) or intrinsic sources (mitochondrial dysfunction, microsomal oxidative stress)—the cell's first defensive response is to increase production of endogenous antioxidants. Aβ, which can be generated rapidly from constitutively expressed APP through upregulation of BACE1 and γ-secretase, serves as an inducible antioxidant system. The cell sacrifices synaptic function to purchase oxidative protection. This compensatory function of Aβ as an antioxidant has profound implications. It explains why anti-amyloid therapies, which reduce Aβ levels, can paradoxically accelerate cognitive decline in some patients. By removing the endogenous antioxidant system that the brain has mobilized in response to lipid peroxidative stress, these therapies leave the brain more vulnerable to further oxidative damage. The lipid peroxidative cascade that triggered the compensatory Aβ response remains unaddressed. This is particularly relevant in the context of APOE4, where the structural inability to form protective disulfide bridges renders the PUFA cargo more vulnerable to peroxidation and thus creates a more potent stimulus for compensatory Aβ production. Huang's monomer depletion hypothesis provides a complementary perspective on the compensatory nature of Aβ in the synaptic microenvironment. Huang proposes that monomeric Aβ, under conditions of normal synaptic activity, serves a physiological function in memory consolidation and in the

dynamic regulation of synaptic strength. Specifically, Aβ monomer is hypothesized to regulate NMDA receptor trafficking, to modulate long-term potentiation through interactions with PSD95 and related synaptic scaffolding proteins, and to serve as a ligand for cell surface receptors that regulate synapse-to-nucleus signaling. When Aβ production becomes elevated as a compensatory response to excitatory insufficiency or oxidative stress, the monomeric Aβ that would normally diffuse freely in the synaptic cleft and exert these regulatory functions instead becomes rapidly incorporated into oligomers and sequestered in endosomal compartments. The result is a paradoxical loss of the normal, beneficial Aβ signal precisely when the synapse most needs it—during conditions of stress. The transition from compensatory to pathological becomes, in Huang's framework, a tragedy of misguided cellular logic. The synapse, detecting a deficit in normal Aβ monomer signaling (whether because monomers are being sequestered or because endosomal generation of Aβ is outpacing monomer diffusion), attempts to increase production further. But the increased production only accelerates oligomerization and sequestration, deepening the monomer depletion. The synapse enters a pathological cycle: attempting to restore a normal signal (Aβ monomer) through a mechanism (increased Aβ production) that inherently prevents the signal from accumulating in the correct location. These four frameworks converge on several fundamental insights about the compensatory paradigm. First, they establish that the hallmark pathological features of Alzheimer's disease—Aβ plaques and neurofibrillary tangles—are not primary causes of disease but rather secondary, compensatory responses to a more fundamental pathogenic insult. In Moosmann's framework, the primary insult is excitatory insufficiency. In Rappoport's framework, it is allostatic overload and metabolic dysfunction. In Ramsden's framework, it is lipid peroxidation. In Huang's framework, it is the dysfunction of synaptic plasticity mechanisms that normally depend on Aβ monomer signaling. Second, they establish that anti-amyloid therapies are mechanistically misguided. Removing Aβ without addressing the upstream cause of its compensatory upregulation is equivalent to treating a fever by destroying the immune system that is producing the fever-inducing cytokines. The fever (Aβ accumulation) is not the disease; it is a symptom of the disease. Treating the symptom while leaving the underlying cause intact is not only ineffective but potentially harmful. Third, these frameworks identify the adaptive-to-maladaptive transition as the critical juncture in disease progression. For a period—potentially years or decades—the compensatory responses of Aβ production, tau phosphorylation, and neuroinflammation genuinely help the cell cope with the primary pathogenic insult. Only when these compensatory responses persist past the point at which they can be metabolically sustained, or when their molecular mechanisms become mechanistically overwhelming, do they transition into pathology. Understanding the variables that govern this transition—the intensity and chronicity of the primary insult, the metabolic reserves available to the cell, the efficiency of the degradative systems that normally clear aggregated proteins—becomes essential to therapeutic strategy. Fourth, these frameworks suggest that interventions that address the primary pathogenic insult would be far more effective than interventions that target the compensatory response. If the primary insult in a given patient is lipid peroxidation, then dietary modification to reduce PUFA oxidation, supplementation

with antioxidants or APOE isoform-specific modulators, and restoration of the lipid-protecting disulfide bridge machinery would be appropriate. If the primary insult is excitatory insufficiency, then restoration of glutamatergic tone through NMDA receptor modulators, enhancement of dendritic spine density through neurotrophic factors, or promotion of exercise-induced neuroplasticity would be appropriate. If the primary insult is allostatic overload, then stress reduction, metabolic optimization, and sleep enhancement would be appropriate. These are not anti-amyloid strategies; rather, they are strategies aimed at addressing the root cause that triggered the amyloid compensatory response in the first place. The compensatory paradigm also clarifies the heterogeneity of Alzheimer's disease. The clinical presentations observed in different patients may reflect differences in which primary pathogenic insult is dominant. A patient whose disease is primarily driven by lipid peroxidation may respond very differently to therapeutic intervention than a patient whose disease is primarily driven by excitatory insufficiency. The amyloid that accumulates in both patients is not the cause of their disease; it is a sign of the underlying cause. Diagnosis and treatment based primarily on amyloid status, as the current paradigm encourages, is thus fundamentally misaligned with pathophysiology. Finally, the compensatory paradigm offers an explanation for the clinical observation that many individuals accumulate substantial pathological amyloid burden without developing cognitive impairment. These asymptomatic amyloid-positive individuals are hypothesized to have engaged successful compensatory responses without the compensatory response itself becoming pathologically overwhelming. The amyloid is present because the compensatory machinery is intact and working. The cognitive preservation occurs because the compensatory response has not yet transgressed from beneficial to harmful. From this perspective, the goal of therapy in asymptomatic amyloid-positive individuals would be to support the integrity of the compensatory system and to address the underlying cause of compensation, not to reduce amyloid levels and thereby disable the compensation. ---

11. The Cytoskeletal Collapse Node

The structural integrity of the neuronal cytoskeleton—and in particular the dynamic equilibrium of actin filaments that comprise the core of dendritic spines and the stabilizing function of microtubules that support axonal and dendritic architecture—emerges as a convergent node where four frameworks (Ramsden, Margolis, Huang, and Shatz/Brott) identify dysregulation of the same molecular targets and mechanisms. The actin filament system undergoes catastrophic remodeling, dendritic spines collapse and are eliminated, and the microtubule-organizing center becomes dysfunctional. These changes represent not merely consequence but active pathogenic mechanism—they drive the loss of synaptic connectivity that underlies the cognitive impairment characteristic of Alzheimer's disease. Understanding this cytoskeletal collapse node is essential to comprehending how molecular perturbations at the endosomal or immunological level ultimately translate into the anatomical and functional destruction of neuronal circuits. The Ramsden

framework establishes the first arm of the cytoskeletal collapse mechanism through the dysregulation of the cofilin-actin system. Cofilin is a small actin-binding protein that severs actin filaments, promoting depolymerization and the dynamic turnover essential for normal synaptic function. Cofilin is normally held in an inactive state through phosphorylation by LIM domain kinase 1 (LIMK1). The kinase activity of LIMK1 is inhibited by the Slingshot phosphatase family (SSH1/SSH2), which dephosphorylates and inactivates LIMK1, thereby allowing cofilin to become active and to regulate actin dynamics. This system creates a switch: LIMK1 active state leads to actin stabilization through cofilin inactivation, while LIMK1 inactivation leads to actin depolymerization through cofilin activation. When the Reelin-ApoER2-Dab1 pathway is disrupted by oxidized ApoE, as described in the Ramsden framework, the consequence is GSK3β hyperactivation. GSK3β directly phosphorylates and inactivates SSH phosphatases. The inactivation of SSH phosphatases means that LIMK1 remains constitutively active. Active LIMK1 phosphorylates cofilin, keeping it in its inactive, unphosphorylated state unable to sever actin filaments. The initial consequence is actin filament stabilization, which is structurally reinforced. However, this stabilization is only the proximate consequence. The deeper consequence is that the normal, dynamic regulation of actin filament turnover is lost. Dendritic spines require continuous, regulated actin polymerization and depolymerization to maintain their shape and to support the mechanical changes necessary for synaptic strengthening and weakening. When cofilin is chronically inhibited and the actin system becomes locked in a stable state, the capacity for activity-dependent morphological remodeling is lost. Moreover, the Ramsden framework identifies a second consequence of LIMK1 hyperactivation that occurs downstream of its effect on cofilin. The same kinase that phosphorylates cofilin also phosphorylates additional targets, including the sodium-potassium ATPase and various other signaling proteins. The hyperactivation of this kinase in the context of oxidative stress and calcium dysregulation creates a state of dysregulated protein phosphorylation that affects multiple cellular systems simultaneously. The Margolis framework contributes a second pathway to cytoskeletal collapse, one that directly attacks actin dynamics through the Ephexin5- RhoA signaling axis. Ephexins are Rac guanine nucleotide exchange factors (GEFs) that promote the conversion of RhoA from its GDP-bound (inactive) to its GTP-bound (active) state. In the context of dendritic spines, Ephexin5 is particularly relevant. The Margolis framework emphasizes that several Alzheimer's disease risk factors—including aging, APOE4 status, and neuroinflammatory signals—lead to activation of Ephexin5. When Ephexin5 is activated, it catalyzes the GDP-to-GTP conversion of RhoA. Active RhoA binds to Rho-associated kinase (ROCK) and activates its kinase domain. Active ROCK phosphorylates a different actin-binding protein, myosin light chain kinase (MLCK), and also directly phosphorylates the myosin II light chain. The consequence of ROCK activation is contraction of the actin- myosin system. In dendritic spines, which are small, bulbous protrusions supported primarily by actin filaments and relatively little cytoskeletal support otherwise, sustained contraction of the actin-myosin system leads inevitably to spine collapse. The spine neck constricts, the spine head shrinks, and the postsynaptic density—the electron-dense structure containing hundreds of NMDA and AMPA receptors and

their scaffolding proteins—loses its structural support. The postsynaptic density ruptures or is remodeled, and the synapse is functionally eliminated. This dendritic spine collapse occurs with stunning speed when ROCK activation is sufficient; spines can collapse from extended to absent over the course of hours. The Margolis framework identifies multiple upstream triggers for Ephexin5 activation. These include oxidative stress (which can lead to oxidative activation of the Ephexin5-RhoA pathway), certain patterns of neuroinflammatory signaling (particularly those mediated by microglial- derived TNF and IL-1), and dysregulation of the intracellular calcium dynamics that normally tightly controls RhoA signaling. Importantly, Margolis notes that RhoA hyperactivation represents a form of pathological negative regulation—a gain of inhibitory signaling on cytoskeletal dynamics —that is distinct from the loss-of-function mechanisms emphasized in other frameworks. The Huang framework contributes a third perspective on cytoskeletal collapse through the lens of competitive synaptic plasticity. In Huang's model, dendritic spines at each synapse engage in competition for limited synaptic resources—including neurotrophic factors, synthesized proteins, and metabolic substrates. Spines that are actively stimulated receive these resources; spines that are less active are deprived and retract. Under normal circumstances, this competition is dynamic and reversible; spines that lose competition transiently can re-enter competition and grow again. However, Huang emphasizes that in Alzheimer's disease, the competitive landscape becomes pathologically skewed. The loss of normal Aβ monomer signaling creates a state in which active spines cannot consolidate their strength, and quiet spines cannot maintain their baseline stability. The result is that the synaptic population becomes unstable; spines that lose activity are no longer able to recover it. Huang identifies a molecular mechanism for how the loss of Aβ monomer signaling translates into altered competition. Aβ monomer interacts with PSD95 and related postsynaptic density proteins, promoting synaptic efficacy and calcium signaling. When Aβ monomer is depleted (sequestered in endosomal compartments, as discussed in previous chapters), the signaling that normally strengthens active synapses is lost. Simultaneously, the loss of NMDA receptor signaling from excitatory insufficiency (as described by Moosmann) further impairs the calcium and kinase signaling that normally promotes synaptic maintenance. Spines that depend on this signaling for their structural and functional stability are eliminated. The competitive elimination of synapses in Huang's framework is thus not a random pruning but a specific consequence of the loss of the normal synaptic signaling that supports active spine maintenance. A particularly striking convergence emerges when the Shatz/Brott framework is considered alongside the actin collapse mechanisms. The Shatz/Brott framework identifies a microglial-mediated synaptic pruning cascade initiated by complement deposition on synapses marked for elimination. The mechanism involves the binding of the complement protein C4d to the presynaptic terminal, followed by recognition of C4d-tagged synapses by microglial complement receptors (particularly CR3, which binds iC3b, and CR1, which binds C4b) and the related immune receptor TREM2. The microglia engulfing the synapse must overcome the cytoskeletal resistance of the synapse; specifically, the actin filament scaffold of the dendritic spine must be dismantled to allow the spine to be phagocytosed. Critically, the Shatz/Brott framework identifies a molecular mechanism that links

synaptic tagging (C4d deposition) to cytoskeletal remodeling (actin dismantling): the interaction between microglial integrin receptors and the extracellular matrix. When microglial integrins engage with extracellular matrix proteins, they trigger signaling cascades that activate RhoA in the microglial cell. But more importantly, they can also trigger trans-synaptic signaling that activates RhoA in the neuronal synapse being engulfed. This trans-synaptic signaling, mediated through cell-cell adhesion molecules and their intracellular signaling partners, creates conditions favorable for the actin collapse that precedes synaptic elimination. The convergence of these mechanisms—Ramsden's LIMK1-mediated cofilin inactivation, Margolis's Ephexin5-RhoA-ROCK-mediated actin-myosin contraction, Huang's competitive plasticity-driven synaptic elimination, and Shatz/Brott's complement-tagged microglial pruning with its attendant RhoA activation—creates a pathological state in which actin filament dynamics are thoroughly dysregulated. Multiple independent mechanisms are simultaneously driving actin collapse, from different angles. The consequence is remarkably robust: dendritic spines are eliminated with high efficiency. The cytoskeletal collapse node also involves microtubule dysregulation, though through mechanisms somewhat distinct from actin dysregulation. Tau, the microtubule-associated protein that is hyperphosphorylated in Alzheimer's disease, normally binds to and stabilizes microtubules. However, hyperphosphorylated tau shows reduced binding affinity for microtubules and instead forms insoluble filaments with itself. The consequence is that microtubules lose their stabilizing protein and become prone to depolymerization. In addition, Ramsden's framework emphasizes that GSK3β not only inactivates cofilin through SSH phosphatase inactivation but also directly phosphorylates tau. The Moosmann framework adds that the calcium dysregulation associated with NMDA hypofunction activates additional kinases, including calcium-calmodulin-dependent protein kinase II (CaMKII) and calpains, which also phosphorylate tau at many sites. The result is hyperphosphorylated tau on a global scale, affecting microtubule stability throughout the neuron. The consequence of microtubule dysregulation is particularly severe in the axon and in the proximal dendrites, where microtubules bear the primary burden of supporting the tubular structure against intracellular pressure and against the mechanical stresses of axonal transport. When microtubules depolymerize, they cannot maintain the structural architecture, and the axon becomes vulnerable to damage. This has profound consequences for axonal transport. Anterograde transport of synaptic vesicles and other cargo is dependent on stable microtubule highways; when these are disrupted, the delivery of synaptic proteins to the presynaptic terminal fails. Retrograde transport of signaling molecules (including neurotrophic factor signaling) from the synapse back to the soma becomes impaired, leading to withdrawal of trophic support. The synapse and its supporting structural architecture are thus attacked simultaneously from two directions: the actin filament scaffold is actively collapsed, and the microtubule support structure is passively destabilized. The temporal sequence of cytoskeletal collapse is worthy of particular attention. The initial events appear to be the lipid peroxidation-driven disruption of the Reelin pathway (Ramsden) and the activation of Ephexin5- RhoA signaling (Margolis), both of which are driven by oxidative stress and dysregulated calcium signaling. These lead to early changes in dendritic spine

morphology and initial actin dysregulation. Over time, as the primary pathogenic insults persist and the compensatory responses fail, the additional mechanisms emphasized by Huang and Shatz/Brott come into play. The synaptic population becomes increasingly engaged in competitive elimination, and microglia-mediated pruning adds an active immune mechanism to the structural collapse. By the time the pathology is fully developed, the cytoskeleton is being attacked from multiple directions simultaneously, and reversal becomes extremely difficult because the upstream causes of each attack must be individually addressed. Table 2: Cytoskeletal Collapse Convergence Map

Framework Mechanism Primary Target Initiating Signal Consequence

Ramsden LIMK1 hyperactivation; cofilin inactivation Actin filament dynamics GSK3β hyperactivation (from Reelin pathway disruption) Loss of activity- dependent actin remodeling; spine destabilization Margolis Ephexin5-RhoA- ROCK activation; myosin light chain phosphorylation Actin-myosin contraction Oxidative stress, neuroinflammatory signals, calcium dysregulation Rapid dendritic spine collapse and elimination Huang Competitive synaptic plasticity dysregulation Synaptic stability competition Loss of Aβ monomer signaling; NMDA hypofunction Progressive elimination of weak or inactive spines Shatz/Brott Microglial complement- dependent pruning; trans-synaptic RhoA signaling Synaptic tags and dendritic spine structure C4d deposition on synapses; microglial engulfment signals Active elimination of tagged synapses; integration of immune and structural collapse mechanisms The implications of the cytoskeletal collapse node are both sobering and clarifying. The loss of synaptic connectivity in Alzheimer's disease, which correlates more tightly with cognitive decline than any other neuropathological feature, is not a passive consequence of Aβ toxicity or amyloid-mediated injury. Rather, it is an active process orchestrated through multiple independent mechanisms that all converge on the actin and microtubule cytoskeleton. Understanding that the collapse is active, overdetermined, and driven from multiple angles simultaneously explains why simple interventions to block any single pathway have failed. Blocking RhoA activation alone, for instance, would not prevent cofilin-mediated actin depolymerization or microglial pruning. Blocking microglial complement signaling would not prevent oxidative stress-driven actin collapse. The true solution would require simultaneous intervention at multiple points in the cytoskeletal pathogenic network. ---

12. The Neuroimmune Interface

The engagement of the innate immune system in Alzheimer's disease progression represents a critical juncture where the neuronal pathology described in previous chapters intersects with immune-mediated pathology. Two frameworks (Huang and Shatz/Brott) and portions of the Moosmann and Rappoport frameworks establish that microglial activation and complement-mediated synaptic pruning are not secondary inflammatory responses but rather active mechanisms of neuronal destruction that integrate seamlessly with the structural and functional

collapse described elsewhere. This chapter maps the neuroimmune interface as a convergent node where the tagging and elimination of synapses occurs through mechanisms that link immune recognition to actin cytoskeletal collapse. The Shatz/Brott framework provides the most comprehensive articulation of the neuroimmune pruning cascade. The authors emphasize that synaptic pruning—the developmental process by which unnecessary synapses are eliminated to refine neural circuits—is normally a tightly regulated process mediated by the complement system. During development, weak or inactive synapses are tagged by deposition of the complement protein C3 (or C4, though C3 is more extensively studied in this context). The C3 deposition marks these synapses for elimination. Microglia, the resident immune cells of the brain, express complement receptors (CR3) that recognize and bind deposited complement. When microglial CR3 engages with C3-tagged synapses, the microglial cell is activated to engulf and digest the synapse, physically removing it from the circuit. This process is essential to normal brain development and synaptic refinement. However, in Alzheimer's disease, this developmental process is pathologically reactivated in the adult brain. The Shatz/Brott framework specifies that the complement protein at the heart of the adult AD pruning cascade is C4d, not C3. C4d is the cleavage product of C4b, the initial product of C4 cleavage in the classical complement pathway. C4d remains covalently bound to the surface of the cell or synapse where C4 was cleaved. In Alzheimer's disease, C4d is deposited on synapses at levels far exceeding those seen in normal aging. The deposition of C4d marks synapses for elimination. Microglial complement receptors (particularly CR1 and CR3) recognize C4d and bound C4b, and binding of these receptors triggers microglial activation, chemotaxis toward the tagged synapse, and phagocytic engulfment. The question of what activates the complement cascade in Alzheimer's disease—what causes C4 to be cleaved and C4d to be deposited on synapses —is addressed by the Shatz/Brott framework through consideration of both direct and indirect mechanisms. Direct activation can occur through the binding of complement factor C1q to altered neuronal surfaces or to accumulated protein aggregates. C1q is the recognition component of the classical complement pathway; when it binds to pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs), it initiates the sequential activation of C1r and C1s proteases, which in turn cleave C4 and C2. Aβ aggregates, oxidatively modified proteins, and phosphorylated tau represent endogenous DAMPs that can activate C1q. Additionally, antibodies bound to neuronal antigens can also activate C1q, particularly if multiple antibodies are bound in close proximity to create a high local density of IgG or IgM. An indirect mechanism for complement activation, emphasized by Shatz/Brott, involves the recognition of neuronal surfaces by pattern recognition receptors other than complement-related receptors. These include TLRs (toll-like receptors), which recognize molecular patterns associated with cellular damage or misfolded proteins. Microglial TLRs can recognize pathogenic Aβ oligomers, hyperphosphorylated tau, and other products of neuronal dysfunction. When microglial TLRs are engaged, they trigger signaling cascades that result in microglial activation, including upregulation of complement components and complement receptors. A recently identified pathway involves the receptor TREM2 (triggering receptor expressed on myeloid cells 2), which directly recognizes and

binds to various ligands including phosphatidylserine (exposed on damaged neuronal membranes), certain lipid species, and modified forms of ApoE. TREM2 engagement on microglia leads to activation of intracellular signaling cascades that result in microglial migration, proliferation, and a pro-inflammatory state. Critically, the Shatz/Brott framework emphasizes that TREM2 signaling is closely linked to complement signaling. TREM2 is expressed on microglial cells alongside complement receptors. Engagement of both TREM2 and complement receptors on the same microglial cell creates a synergistic signal for microglial activation and synaptic engulfment. Furthermore, TREM2 can directly interact with complement receptors, creating a physical and functional link between pattern recognition through TREM2 and complement-mediated synaptic tagging. The integration of this neuroimmune cascade with the cytoskeletal collapse mechanisms described in Chapter 11 is elegantly accomplished through a mechanism that Shatz/Brott term "trans-synaptic signaling." When microglial complement receptors engage with C4d on the presynaptic terminal, and when microglial TREM2 engages with ligands presented on the synaptic surface, the microglial cell undergoes rapid activation and initiates phagocytic engulfment. However, the engagement of microglial receptors with synaptic ligands also triggers signaling cascades within the neuronal synapse being engulfed. These trans-synaptic signals include the activation of neuronal RhoA, the engagement of neuronal TLRs and other pattern recognition receptors, and the triggering of neuronal calcium influx. The consequence is that the dendritic spine receiving the microglial attack simultaneously undergoes the RhoA-mediated actin collapse described in the Margolis framework. This trans-synaptic mechanism is particularly important because it explains how the microglial immune attack on the synapse can be so rapidly destructive. The synapse is not a passive victim being consumed by microglia; rather, the synapse actively participates in its own dismantling in response to immune recognition signals. The actin filament scaffold is actively contracted and depolymerized even as the microglial cell is engulfing the dendritic spine. This creates a situation of remarkable pathological efficiency: the presynaptic terminal and the postsynaptic dendritic spine are simultaneously attacked, from the outside by microglial phagocytosis and from the inside by immune-triggered actin collapse. The Huang framework adds an important perspective on how neuroinflammation integrates with the competitive synaptic plasticity mechanisms described previously. Huang notes that neuroinflammatory signals, particularly those mediated by TNF and IL-1 produced by activated microglia, alter the synaptic competition landscape described in Chapter

11. These cytokines enhance the efficacy of synaptic weakening mechanisms and reduce the efficacy of synaptic strengthening mechanisms. A synapse that is targeted by microglial pruning signals is simultaneously weakened by the effects of local TNF and IL-1 on synaptic plasticity mechanisms. This creates a compounded effect: the synapse is both structurally attacked by microglial phagocytosis and functionally attacked by neuroimmune-mediated inhibition of synaptic strengthening. The Moosmann and Rappoport frameworks add context regarding the upstream triggers for neuroinflammation. Moosmann identifies that the chronic excitatory insufficiency and

the associated calcium dysregulation that characterizes early AD leads to increased production of danger signals and damage-associated molecular patterns. Hypocampal neurons and cortical pyramidal cells experiencing NMDA hypofunction accumulate damaged mitochondria, accumulate protein aggregates, and undergo partial membrane permeabilization—all conditions that expose DAMPs to the extracellular space and to microglial pattern recognition receptors. The result is microglial activation as a secondary consequence of the primary excitatory insufficiency. Rappoport's allostatic load model frames the neuroinflammatory response as initially adaptive—a necessary component of the allostatic response to stress—but becoming pathological when the stress becomes chronic. During an acute stress or injury, microglial activation and complement-mediated elimination of damaged synapses is beneficial; it removes dysfunctional neuronal connections and creates space for compensatory plasticity. However, if the stimulus for microglial activation (the persistence of excitatory insufficiency, the continued accumulation of DAMPs, the ongoing lipid peroxidation) is never resolved, then the microglial activation persists. Microglia transition from a resting, surveillance state to an activated, pro- inflammatory state. The production of TNF, IL-1, and other pro- inflammatory cytokines becomes chronic. Under these conditions, the same microglial response that initially promoted clearing of damaged synapses becomes destructive, eliminating synapses that are still functionally important and driving a transition from adaptive neuroinflammation to pathological neuroinflammation. A critical integration between the neuroimmune interface and the endosomal nexus described in Chapter 9 emerges through consideration of the trafficking of complement components and microglial receptors. The production of complement components, the processing and trafficking of C4 to the synaptic surface, and the localization of complement receptors on microglial cells all depend on endosomal trafficking. When retromer dysfunction and endosomal traffic jams occur (as described by Small), the trafficking of complement components to appropriate intracellular and extracellular sites is impaired. This paradoxically could lead either to decreased complement deposition (if complement proteins fail to reach synapses) or to altered localization of complement components that becomes pathologically dysregulated. Similarly, microglial TREM2 trafficking depends on proper endosomal recycling. When endosomal dysfunction occurs in microglia, TREM2 accumulates in endosomal compartments and becomes unavailable for surface expression. The consequence is complex: the same endosomal dysfunction that impairs neuronal homeostasis also impairs microglial responses, potentially leading to either compensatory upregulation of complement and TREM2 or to dysregulation of their trafficking. The neuroimmune interface also connects to the compensatory paradigm described in Chapter 10. The neuroinflammatory response, including microglial activation and complement deposition, can be viewed as yet another compensatory response to primary pathogenic insults. The microglia attempts to clear dysfunctional neurons and damaged synapses, interpreting the accumulation of Aβ and tau as signals of neuronal death that require immune clearance. However, if the stimulus for Aβ and tau accumulation (the excitatory insufficiency, the lipid peroxidation, the endosomal dysfunction) is not resolved, then the microglial clearing response cannot succeed in restoring homeostasis. The microglia becomes chronically

activated, and the same effectors that were initially beneficial (C4d deposition, TREM2 signaling, complement-mediated synaptic engulfment) become pathological because they are continuously deployed against essentially intact neurons. The question of what determines whether the neuroimmune response transitions from beneficial to pathological is thus intimately connected to the persistence and severity of the primary pathogenic insult. If the primary insult (lipid peroxidation, excitatory insufficiency, endosomal dysfunction) can be resolved, then the neuroimmune response terminates, and the brain recovers. However, in most cases of Alzheimer's disease, the primary insult persists, and the neuroimmune response persists with it, becoming progressively more destructive over time. The implications for therapeutic strategy are significant. Approaches that attempt to immunosuppress the neuroimmune response—inhibiting complement activation, blocking TREM2 signaling, or broadly suppressing microglial activation—address only the downstream consequence of the primary pathogenic insult, not the insult itself. Such approaches might have transient benefit but would likely fail to halt disease progression as long as the primary insult persists. Conversely, approaches that address the primary pathogenic insult (reducing lipid peroxidation, restoring excitatory tone, correcting endosomal trafficking) would be expected to result in resolution of the neuroimmune response as well. The neuroimmune system, viewed from this perspective, is not a problem to be solved but rather a symptom of the fundamental problem that requires resolution. ---

13. The ApoE4 Problem

Apolipoprotein E4 (APOE4) represents perhaps the most consistently replicated genetic risk factor for sporadic Alzheimer's disease, with carriers of the APOE4 allele showing exponentially elevated risk of disease onset and accelerated cognitive decline compared to carriers of APOE3 or APOE2. While the historical amyloid cascade hypothesis has positioned APOE4 as somehow facilitating amyloid accumulation, examination of the eight frameworks presented in this thesis reveals that APOE4 operates through at least eight distinct, mechanistically compatible pathways that together explain its profound neurotoxic effects. This chapter maps these eight mechanisms across the framework landscape and proposes that APOE4 should not be understood as a single-mechanism risk factor but rather as a hub allele whose altered structure affects multiple domains of neuronal function simultaneously. The first and perhaps most fundamental mechanism is emphasized by the Ramsden framework: the structural inability of APOE4 to form protective intermolecular disulfide bridges. The APOE4 protein differs from APOE3 and APOE2 at amino acid positions 112 and 158. APOE3 has cysteine at position 112 and arginine at position 158; APOE2 has cysteines at both positions; APOE4 has arginine at position 112 and arginine at position 158. The presence of a cysteine residue allows the formation of disulfide bonds (covalent crosslinks between cysteine thiol groups) both within the same ApoE molecule and between different ApoE molecules, creating an intermolecular network. These disulfide bridges have a specific structural function: they protect the

polyunsaturated fatty acid cargo from access by oxidative species. The domains of ApoE that contain cysteine residues adopt conformations that shield the bound PUFAs, creating a hydrophobic pocket that is largely inaccessible to water and to aqueous phase reactive oxygen species. In APOE4, the absence of the critical cysteine at position 112 means that this structural protection cannot be achieved. The PUFA cargo transported by APOE4 is significantly more exposed to the aqueous phase, making it substantially more vulnerable to peroxidation by water-soluble oxidizing species including superoxide, hydrogen peroxide, and hydroxyl radicals. The consequence of this increased PUFA vulnerability in APOE4 carriers is that the endosomal lipid peroxidation cascade described in Chapter 9 is initiated at a lower threshold. An APOE4 carrier may accumulate similar or even slightly lower absolute levels of systemic oxidative stress as an APOE3 carrier, yet the APOE4 carrier experiences more severe PUFA peroxidation simply because the protective structure is absent. This explains the counterintuitive observation that APOE4 carriers sometimes show lower blood levels of oxidative stress markers yet have more severe neurodegeneration—the damage from lipid peroxidation is concentrated at the critical site (within the astrocyte-generated ApoE cargo), creating focal regions of extreme peroxidative stress even if systemic stress is moderate. The reactive aldehydes generated by PUFA peroxidation in APOE4 cargo then undergo the Schiff base and Michael addition reactions with lysine and cysteine residues on ApoE and ApoER2, leading to the receptor trapment described in the Ramsden framework. The consequence is the disruption of the Reelin-ApoER2-Dab1 cascade and the initiation of the GSK3β hyperactivation that drives tau hyperphosphorylation and cytoskeletal collapse. The second mechanism involves APOE4's altered interactions with retromer components and its effects on endosomal traffic, as emphasized by the Small framework. The retromer complex depends on its interaction with cargo proteins for its assembly and function. APP and SORL1, both of which are substrate for retrieval from the early endosome, interact with retromer components, and this interaction is isoform-dependent. APOE4 has different binding properties for the retromer complex and for SORL1 compared to APOE3. APOE4 is a weaker activator of retromer-mediated retrieval of certain lipoprotein receptors, particularly LDL receptor-related proteins. The consequence is that when APOE4 is present, the efficiency of endosomal cargo retrieval is compromised even if retromer proteins are present in normal quantities. This creates a state of partial retromer insufficiency specifically in the context of APOE4 expression. The third mechanism involves the direct effects of APOE4 on intraneuronal Aβ42 accumulation, as emphasized by the Gouras framework. Gouras emphasizes that APOE4 enhances the accumulation of intraneuronal Aβ42. The mechanism is thought to involve altered trafficking of APP and/or altered efficiency of BACE1-mediated cleavage of APP in the context of APOE4. However, another component likely involves the altered lipid raft organization created by APOE4. As emphasized in the Rappoport framework, APOE4 creates a different lipid raft organization compared to APOE3. The lipid raft environment within endosomes and synaptic membranes is altered when APOE4 is present. Since APP processing occurs preferentially within lipid raft microdomains, the altered lipid raft composition in APOE4 carriers could lead to altered APP processing kinetics and increased Aβ

generation. The fourth mechanism involves APOE4's effects on the NMDA receptor and on excitatory tone, as emphasized by the Moosmann framework. Moosmann identifies that APOE4 carriers show altered NMDA receptor trafficking and reduced surface expression of functional NMDA receptors compared to APOE3 or APOE2 carriers. The mechanism appears to involve altered membrane lipid composition specifically in the domains where NMDA receptors are localized. Since Moosmann's hypothesis posits that excitatory insufficiency is the primary pathogenic driver, and since APOE4 appears to intrinsically promote a state of reduced excitatory tone, APOE4 carriers begin disease progression from a position of baseline excitatory insufficiency. This creates a situation in which the compensatory upregulation of Aβ production described in Chapter 10 is initiated earlier and at a lower threshold in APOE4 carriers compared to other genotypes. The fifth mechanism involves APOE4's direct effects on lipid raft organization and cellular lipid homeostasis, as emphasized by the Rappoport framework. Rappoport emphasizes that lipid rafts are dynamic structures whose organization depends critically on the proteins present and the lipid composition. APOE4 creates a lipid raft organization that is more densely packed with cholesterol and is more prone to oxidative damage. The consequence is that neurons and glia carrying APOE4 have lipid membrane compartments that are inherently more reactive to oxidative stress. When oxidative stress occurs (from diet, from environmental exposures, from mitochondrial dysfunction, or from aging), the APOE4-associated lipid raft microdomains are more severely damaged than the APOE3-associated microdomains in a comparable APOE3-carrying cell. The sixth mechanism involves APOE4's effects on the actin cytoskeleton and dendritic spine stability, as emphasized by the Margolis framework. Margolis identifies that APOE4 status influences the propensity toward Ephexin5-RhoA-ROCK pathway activation. The mechanism is thought to involve altered signaling through Eph receptors and other receptor tyrosine kinases that are known to interact with ApoE receptors. APOE4 creates a biochemical environment that is more permissive for RhoA activation, potentially because of altered membrane organization or altered signaling protein interactions. The consequence is that dendritic spines in APOE4 carriers are more susceptible to collapse in response to oxidative stress or inflammatory signals. The seventh mechanism involves APOE4's effects on APP processing in endosomal compartments, as emphasized by the Huang framework. Huang identifies that the proteolytic processing of APP is sensitive to the lipid environment and to the pH and ionic conditions of the endosomal microenvironment. APOE4, through its effects on endosomal lipid composition and pH regulation (via effects on v-ATPase as described by Ramsden), alters the kinetics of APP processing. The consequence is that in APOE4 carriers, the rate of Aβ42 generation may be higher than in other genotypes, even when the same proteolytic enzymes are present at comparable expression levels. The eighth mechanism involves APOE4's effects on the complement pathway and on microglial activation, as emphasized by the Shatz/Brott framework. APOE modulates the activation of the classical complement pathway through its interaction with C1q, the recognition component of the complement cascade. APOE3 is a more effective suppressor of complement activation than APOE4. The consequence is that in APOE4 carriers, the complement cascade is more readily activated in

response to protein aggregates and oxidatively modified proteins. This creates a state of enhanced microglial activation and more aggressive complement-mediated synaptic pruning in APOE4 carriers compared to APOE3 or APOE2 carriers. The convergence of these eight mechanisms in APOE4 carriers creates a remarkable state of multisystem vulnerability. An APOE4 carrier simultaneously experiences enhanced lipid peroxidation of ApoE cargo, impaired endosomal traffic, enhanced intraneuronal Aβ42 accumulation, reduced baseline excitatory tone, lipid raft dysorganization that is more susceptible to oxidative damage, enhanced dendritic spine collapse, altered APP processing, and enhanced microglial complement activation. These mechanisms are not redundant; they attack different aspects of the neuronal system. The consequence is that APOE4 carriers have a remarkably low threshold for disease initiation. What might be a tolerable level of lipid peroxidation in an APOE3 carrier becomes pathogenic in an APOE4 carrier because the APOE4 carrier is simultaneously vulnerable across multiple independent pathways. Table 3: APOE4 Mechanisms Across Frameworks

Framework Mechanism Molecular Details Consequence

Ramsden Lack of protective disulfide bridge APOE4 arginine at position 112 prevents cysteine-mediated crosslinking Exposed PUFA cargo vulnerable to severe peroxidation; reactive aldehydes initiate ApoER2 crosslinking; Reelin pathway disruption Small Impaired retromer recycling APOE4 weaker activator of retromer-mediated retrieval Partial retromer insufficiency; endosomal traffic jam; enhanced APP-BACE1 contact; excessive Aβ generation Gouras Enhanced intraneuronal Aβ42 APOE4-associated lipid raft reorganization; altered APP processing kinetics Increased synaptic endosomal Aβ42 accumulation; enhanced intraneuronal phase of pathology Moosmann Reduced excitatory tone; NMDA hypofunction APOE4 alters NMDA receptor trafficking and surface expression; altered membrane lipid composition Baseline excitatory insufficiency; earlier initiation of compensatory Aβ upregulation Rappoport Lipid raft dysorganization; enhanced oxidative vulnerability APOE4 creates denser lipid raft packing; altered cholesterol organization Lipid membranes more susceptible to peroxidative damage; allostatic load more rapidly accumulates Margolis Enhanced dendritic spine collapse susceptibility APOE4 promotes Ephexin5-RhoA-ROCK pathway activation RhoA-mediated actin- myosin contraction more readily triggered; dendritic spines more fragile Huang Altered APP processing; Aβ monomer depletion APOE4-altered endosomal lipid environment; pH dysregulation Enhanced Aβ42 generation rate; more rapid monomer depletion; faster progression of synaptic dysfunction Shatz/Brott Enhanced complement activation APOE4 weaker suppressor of C1q- initiated complement cascade More aggressive microglial activation; enhanced complement- mediated synaptic pruning The implications of this comprehensive APOE4 analysis are profound. APOE4 is not simply a risk factor that makes disease more likely; it is a master regulator of vulnerability that affects nearly every pathogenic mechanism identified in the eight frameworks. The heterozygous APOE3/APOE4 individual has intermediate risk because they express both APOE3 and APOE4 from their two alleles, and the APOE4 molecules can partially activate each mechanism even when

mixed with APOE3. The homozygous APOE4/APOE4 individual has extreme risk because every molecule of ApoE produced is structurally vulnerable and each of the eight pathogenic mechanisms is simultaneously activated. This analysis also clarifies why therapeutic interventions that are effective in APOE3 or APOE2 carriers may be less effective in APOE4 carriers. An intervention that restores endosomal traffic, for instance, would be beneficial in a Small-framework context but might be only partially effective in an APOE4 carrier who is simultaneously vulnerable to all eight mechanisms. A true therapeutic strategy for APOE4 carriers would need to simultaneously address multiple mechanisms—restoration of lipid homeostasis, enhancement of endosomal traffic, reduction of intraneuronal Aβ42, restoration of excitatory tone, protection against lipid raft dysorganization, stabilization of dendritic spines, optimization of APP processing, and modulation of complement activation. The extraordinary burden of APOE4 thus necessitates a correspondingly multifaceted therapeutic approach. ---

14. Broader Network Convergences and Tensions

Beyond the five convergence nodes identified in Chapters 9-13, the eight frameworks reveal several additional convergent molecular mechanisms and molecular players that contribute to the unified architecture of Alzheimer's disease pathogenesis. Simultaneously, these frameworks contain points of genuine tension—areas where they make incompatible predictions or where the mechanisms proposed by one framework appear to contradict those proposed by another. This chapter maps both the convergences and the tensions, acknowledging both the remarkable degree of integration achieved by examining the frameworks as a network and the genuine scientific uncertainty that remains.

Additional Convergences: Epigenetic and Transcriptional

Dysregulation Multiple frameworks allude to epigenetic and transcriptional changes that drive disease progression, though none provides an exhaustive epigenetic account. The Moosmann framework emphasizes that the transition from compensatory to maladaptive states involves progressive changes in gene expression. The chronic activation of calcium-calmodulin-dependent kinase signaling, triggered by NMDA hypofunction and the resulting calcium dysregulation, leads to phosphorylation and activation of CREB (cAMP response element binding protein), which in turn drives altered transcription of multiple genes including increased BACE1 expression and altered expression of NMDA receptor subunits. Over time, this pattern of CREB activation becomes pathological; what was initially an adaptive transcriptional response becomes excessive. The Rappoport framework emphasizes epigenetic changes, particularly DNA methylation changes at promoter regions, that occur in response to allostatic stress. During the adaptive phase of the

allostatic response, DNA methylation patterns change in response to stress signaling, altering the expression of genes involved in stress response. The histone deacetylase HDAC6, for instance, is upregulated in response to cellular stress; it deacetylates histone proteins and transcription factors, altering chromatin structure and gene expression patterns. In the maladaptive phase, these epigenetic changes become locked in place, creating a disease-associated transcriptional landscape that is difficult to reverse. A critical epigenetic mechanism that emerges across multiple frameworks, though most explicitly discussed in the context of aging and genetic risk, involves changes in the expression and activity of small RNAs, particularly microRNAs (miRNAs) and piRNAs (PIWI-interacting RNAs). Several of the frameworks mention in passing that miRNA dysregulation occurs in Alzheimer's disease, affecting the stability of mRNAs encoding APP, tau, presenilin, and multiple other AD-related genes. The Huang framework notes that miR-134, a microRNA that regulates the size and stability of dendritic spines through its effects on Limk1 mRNA, is dysregulated in Alzheimer's disease. The Ramsden framework mentions that let-7 miRNAs, which regulate the expression of genes involved in cellular stress responses and metabolic homeostasis, show altered expression in APOE4 carriers. piRNAs and siRNAs represent an additional layer of epigenetic regulation that, while not extensively detailed in any single framework, appears across multiple frameworks through discussions of transposable element dysregulation. The reactivation of transposable elements, particularly LINE-1 elements, occurs in the brains of Alzheimer's disease patients. This reactivation is thought to be associated with loss of piRNA-mediated silencing of transposable elements. The consequence is that transposable element sequences are transcribed, and the resulting RNA sequences can interact with genes involved in neuronal function, potentially disrupting their normal expression. Some frameworks suggest that LINE-1 reactivation may drive production of aberrant proteins that contribute to neurodegeneration, while others suggest that the disruption of normal gene expression caused by LINE-1 transposition may be the primary pathogenic mechanism. The integrated epigenetic-transcriptional picture, assembled from hints across multiple frameworks, suggests that Alzheimer's disease involves progressive dysregulation of the transcriptional and epigenetic landscape. The initial dysregulation is adaptive—genes involved in stress response and compensatory mechanisms are upregulated; genes involved in normal synaptic function are downregulated. However, if the stress persists, the dysregulation persists, and what was adaptive becomes pathological. miRNA dysregulation amplifies these transcriptional changes; let-7 downregulation might lead to loss of metabolic homeostasis; miR-134 dysregulation might lead to dendritic spine instability. Reactivation of transposable elements adds noise and further disruption to the transcriptional landscape. The cumulative effect is a brain in which the normal patterns of gene expression are so thoroughly disrupted that recovery becomes progressively less likely.

Additional Convergences: SORL1, VPS26b, WASH Complex, and the

Trafficking Node The Small framework emphasizes the critical role of SORL1 (sortilin-related receptor 1) as a key node in endosomal trafficking. SORL1 functions as a retromer-dependent transporter that shuttles APP and BACE1 through the endosomal system, and mutations or loss-of-function variants in SORL1 are associated with increased Alzheimer's disease risk. The Ramsden framework, in discussing the recovery of endosomal homeostasis, notes that SORL1-mediated retrograde trafficking of apolipoprotein receptors is essential to restoring proper lipid distribution. The Gouras framework acknowledges that SORL1 function is critical to controlling intraneuronal Aβ42 levels. VPS26b, a variant of the VPS26 protein component of the retromer complex, emerges as a critical node across frameworks. VPS26b mutations are associated with Alzheimer's disease risk. The Small framework emphasizes that VPS26b has specific substrate selectivity compared to VPS26a; certain cargos, including apolipoprotein receptors, preferentially interact with the VPS26b-containing retromer complex. Loss of VPS26b function thus disproportionately affects the trafficking of lipid receptors, exacerbating lipid homeostasis disruption. The WASH complex (Wiskott-Aldrich syndrome protein and SCAR homologs) is mentioned briefly in the Small framework as a regulator of actin dynamics in endosomal compartments. The WASH complex nucleates actin filaments within endosomes, and these actin filaments are essential to the mechanical processes of endosomal maturation, cargo sorting, and the scission of transport vesicles. Dysregulation of the WASH complex could contribute to both the trafficking jam described by Small and the actin dysregulation described by Margolis and Ramsden, creating a convergence point between the endosomal and actin pathways. The convergence of SORL1, VPS26b, and WASH as trafficking nodes suggests that Alzheimer's disease involves dysfunction across the entire endosomal trafficking system, not just at the level of retromer assembly but across the full spectrum of endosomal maturation, cargo sorting, and actin- dependent mechanical processes.

Additional Convergences: Braak Staging and Temporal Progression

All eight frameworks must, to some degree, account for the well-established Braak staging system, which describes a stereotyped progression of neurofibrillary pathology across brain regions over time. The pathology begins in the locus coeruleus and entorhinal cortex (Braak stages I-II), progresses through the hippocampus and surrounding temporal structures (Braak stages III-IV), and eventually reaches the neocortex (Braak stages V- VI). Each framework implicitly or explicitly maps

its proposed molecular pathology onto this anatomical progression. The Gouras framework most explicitly engages with Braak staging, emphasizing that intraneuronal Aβ42 accumulation follows the same anatomical progression as tau pathology, preceding extracellular plaques by years to decades. The Ramsden framework notes that the locus coeruleus, which is affected first in Braak staging, is particularly vulnerable to the ApoER2-lipid peroxidation mechanism because of its unique position as the main source of noradrenergic input to the entire brain. Noradrenergic neurons are metabolically demanding and particularly vulnerable to oxidative stress. The Moosmann framework emphasizes that the locus coeruleus is also a region where glutamatergic-GABAergic balance is particularly vulnerable, making it susceptible to the excitatory insufficiency that Moosmann proposes as primary. The convergence suggests that the anatomical progression described by Braak staging is not arbitrary but rather reflects the differential vulnerability of specific brain regions to the molecular insults identified across the eight frameworks. The locus coeruleus and entorhinal cortex are vulnerable because they combine high metabolic demand, particular sensitivity to APOE4-related lipid peroxidation, and particular dependence on glutamatergic inputs. Once pathology initiates in these regions, it spreads through anatomically connected networks—following not just anatomical connectivity but also the kinetics of the molecular pathogenic processes. For example, Aβ42 oligomers generated in the locus coeruleus may spread anterogradely along axons to the hippocampus, seeding further Aβ42 generation. Tau hyperphosphorylation initiated by GSK3β hyperactivation in vulnerable regions may spread trans-synaptically to connected neurons, progressively enlarging the circle of affected tissue. Genuine Tensions: The Aβ Question Despite the remarkable convergence achieved across the eight frameworks, one fundamental tension remains unresolved: the role of amyloid-beta in Alzheimer's disease pathogenesis. Four frameworks (Moosmann, Rappoport, Ramsden, and Huang) explicitly conceptualize Aβ as a compensatory response to a primary pathogenic insult, implying that Aβ accumulation is a consequence, not a cause, of disease. These frameworks make the prediction that anti-amyloid interventions should be either ineffective or potentially harmful. In contrast, the Gouras, Small, and Shatz/Brott frameworks, while not endorsing the classical amyloid cascade hypothesis, attribute significant pathogenic roles to Aβ. Gouras emphasizes that intraneuronal Aβ42 accumulation is toxic to synapses, causing direct structural and functional damage before extracellular plaques form. Small emphasizes that the generation of Aβ is a consequence of retromer dysfunction, but that the accumulated Aβ contributes to disease progression through effects on synaptic function and through engagement of immune receptors. Shatz/Brott identify that Aβ can act as a DAMP, triggering C1q-mediated complement activation and thus contributing to the neuroimmune cascade. The tension here is not easily resolved by the frameworks themselves. An APOE4 carrier could simultaneously experience Aβ accumulation as a compensatory response to excitatory insufficiency or lipid peroxidation (as posited by Moosmann, Rappoport, and Ramsden) and also experience direct toxicity from accumulated intraneuronal Aβ42 (as posited by Gouras) and involvement of Aβ in immune activation (as posited by Shatz/Brott). There is, in principle, no contradiction: Aβ could be both compensatory and toxic, depending on context, location, and

degree of accumulation. However, the frameworks do make different predictions regarding the therapeutic efficacy of anti-amyloid interventions. If Aβ is primarily compensatory, anti- amyloid therapy should be ineffective or harmful. If Aβ is directly toxic (as in Gouras) or acts as a DAMP triggering immune damage (as in Shatz/Brott), anti-amyloid therapy should be effective, at least in reducing the amyloid-specific pathogenic mechanisms. The empirical evidence from recent anti-amyloid clinical trials suggests that anti-amyloid monoclonal antibodies (aducanumab, lecanemab, donanemab) produce modest, statistically significant slowing of cognitive decline in early symptomatic and asymptomatic amyloid-positive individuals. The effect size is remarkably small—on the order of 30% slowing of decline over 18 months —and is accompanied by worrisome adverse events (amyloid-related imaging abnormalities, including microhemorrhages). This empirical pattern is difficult to reconcile with simple interpretations of either the compensatory hypothesis or the toxicity hypothesis. If Aβ is purely compensatory, some slowing should not occur. If Aβ is the primary pathogenic driver, the slowing should be more dramatic. The observed pattern—modest slowing with concerning toxicity—suggests either that Aβ plays a minor role in the pathogenic cascade (consistent with the compensatory hypothesis) or that the anti-amyloid antibodies are clearing Aβ incompletely, leaving sufficient Aβ for some toxicity to continue while removing enough Aβ to impair the compensatory response. This tension may ultimately require resolution through more detailed mechanistic studies rather than through abstract theoretical arguments. Future research might determine whether intraneuronal Aβ42 accumulation is genuinely toxic to the synapse or whether it represents a contained compensatory response. It might determine whether the transition from asymptomatic amyloid positivity to symptomatic cognitive decline involves further Aβ accumulation or whether it involves the failure of compensatory mechanisms to cope with other, non-amyloid pathogenic insults. The frameworks presented in this thesis do not fully resolve this tension, but they frame it precisely, identifying the key empirical questions that must be answered. Genuine Tensions: The Tau Question A second tension, related to but distinct from the Aβ question, concerns the role of tau in disease causation versus disease consequence. The Ramsden framework explicitly conceptualizes tau hyperphosphorylation as a consequence of GSK3β hyperactivation, which is itself a consequence of ApoER2 disruption by oxidized ApoE. Tau hyperphosphorylation is not presented as the primary pathogenic event but rather as a downstream effector of lipid peroxidation. The Moosmann framework similarly presents tau hyperphosphorylation as a compensatory response to calcium dysregulation and excitatory insufficiency, occurring as the cell attempts to stabilize microtubules in the face of metabolic stress. However, the Gouras framework identifies intraneuronal tau accumulation and tau modifications as independently pathogenic. Gouras notes that tau modifications, particularly the generation of pseudo-phosphorylated tau (tau with non-phosphorylatable arginine substitutions at phosphorylation sites), may be pathogenic through mechanisms distinct from hyperphosphorylation. These modifications may represent proteolytic cleavage events or other post-translational modifications that impair tau function. Additionally, Gouras proposes that tau can act as a prion-like agent, spreading from neuron to neuron through trans-synaptic propagation. The tension

between these views—tau as consequence versus tau as cause —is partially resolved by noting that tau could be both. Tau hyperphosphorylation, initiated as a compensatory response, could become pathogenic when excessive and when it reaches a threshold beyond which microtubule stabilization is overwhelmed by tau filament polymerization. Tau spreading, initiated when intraneuronal tau levels exceed the capacity of degradative systems, could amplify and propagate pathology to neighboring neurons. The frameworks are not necessarily contradictory; rather, they emphasize different aspects of a complex process. However, the tension does have therapeutic implications. If tau is purely consequential to the primary pathogenic insult, then anti-tau therapies (antibodies against tau, compounds that promote tau clearance) would not address the root cause and might even be counterproductive if tau plays compensatory roles. If tau is independently pathogenic, anti-tau therapies might produce benefits even without addressing upstream causes. The empirical evidence remains limited; tau-targeting immunotherapies (including passive immunization against phosphorylated tau and active immunization approaches) are in early clinical development, and their efficacy remains uncertain. Genuine Tensions: APOE4 Gain-of-Function versus Loss-of-Function The frameworks differ somewhat in their emphasis regarding whether APOE4's pathogenicity derives from a gain of toxic function or from a loss of protective function. The Ramsden framework explicitly frames APOE4 as a loss of the protective disulfide bridge—APOE4 lacks a structure that APOE2 and APOE3 possess. This is straightforwardly a loss-of-function mechanism. Similarly, the Moosmann framework emphasizes that APOE4 reduces excitatory tone, a loss of function. The Rappoport framework emphasizes that APOE4 creates a lipid raft environment that is more vulnerable to oxidative damage, which could be framed as a loss of oxidative protection. However, the Margolis framework suggests a gain of function: APOE4 actively promotes RhoA activation and dendritic spine collapse. This is not merely a loss of protective function; it is an active, deleterious function. Similarly, the Shatz/Brott framework could be interpreted as APOE4 gaining a pro-complement function—APOE4 is a weaker suppressor of complement activation, which could be viewed as a loss of suppression, but it could also be viewed as an active enhancement of complement activation relative to the default state. The distinction between loss-of-function and gain-of-function has implications for therapeutic strategy. If APOE4 pathogenicity is purely loss- of-function, therapeutic strategies might focus on providing the missing function—restoring disulfide bridge formation through chemical modification, restoring excitatory tone through NMDA modulators, or restoring antioxidant protection through increased antioxidant supplementation. If APOE4 pathogenicity involves gain of function, then therapeutic strategies might focus on inhibiting the toxic function—blocking RhoA activation in APOE4 carriers, inhibiting complement activation, or suppressing pro-inflammatory signaling. These strategies would be partially incompatible; the optimal strategy would require addressing both the loss-of-protection and the gain-of-toxicity components. The empirical evidence suggests that both mechanisms are operative. APOE4 carriers with high antioxidant intake show improved outcomes, suggesting that loss of antioxidant protection is significant. However, APOE4 carriers also show worse outcomes with pro-inflammatory insults, suggesting that APOE4 also actively promotes

pathogenic processes. The tension likely reflects the multi-faceted nature of APOE4's effects; it is simultaneously a loss-of-function allele (lacking protective structures) and a gain-of-function allele (actively promoting pathogenic processes). Synthesis of Convergences and Tensions The broader network of convergences and tensions reveals that Alzheimer's disease is not a monolith but rather a network phenomenon with multiple convergent pathogenic arms. The eight frameworks, taken together, identify pathogenic mechanisms operating at the level of lipid chemistry (peroxidation), membrane biology (lipid rafts, endosomal trafficking), receptor signaling (ApoER2, NMDA receptors, TREM2), kinase cascades (GSK3β, LIMK1, ROCK), cytoskeletal dynamics (actin filaments, microtubules), gene expression (transcriptional dysregulation, epigenetic changes), synaptic plasticity (competitive plasticity, long-term potentiation), and immune function (complement activation, microglial pruning). No single framework captures this entire landscape; the unity of the disease emerges only when the frameworks are examined as an integrated network. The tensions identified in this chapter—regarding the roles of Aβ and tau, the loss-of-function versus gain-of-function nature of APOE4, and the mechanisms of pathogenic spread—represent genuine scientific uncertainties that cannot be fully resolved within the current theoretical frameworks. These tensions should not be viewed as weaknesses in the frameworks but rather as insights into where future research must focus. The frameworks that constitute this thesis have achieved remarkable convergence on the core pathogenic mechanisms; the remaining tensions exist at the margins and likely require empirical investigation to resolve. ---

15. The Emergent Network Architecture

Viewed in isolation, each of the eight frameworks examined in this thesis offers a partial but sophisticated account of Alzheimer's disease pathogenesis. Viewed as an integrated network, however, they reveal an architecture of neurodegeneration of remarkable complexity and coherence. This final synthesis chapter maps the full network—describing how all eight frameworks interconnect, proposing a temporal staging model for disease progression, and identifying the central organizing principle: Alzheimer's disease is fundamentally a disease of network failure, in which multiple independent pathogenic mechanisms converge sequentially on shared anatomical and molecular nodes, progressively destroying the structural and functional integrity of neural circuits until cognitive and behavioral collapse becomes inevitable. The Convergent Network Architecture The eight frameworks identify six convergent nodes or hubs within the broader network of Alzheimer's disease pathogenesis: The Endosomal Nexus (Chapter 9): The early endosome is the critical anatomical compartment where lipid peroxidation (Ramsden) disrupts receptor trafficking, where retromer dysfunction (Small) jams endosomal recycling, where intraneuronal Aβ42 accumulates in MVBs (Gouras), and where APP processing dysregulation (Huang) creates sequestered, inaccessible Aβ. This nexus integrates the molecular perturbations from four distinct frameworks into a single anatomical compartment. The Cytoskeletal Collapse

Node (Chapter 11): The actin and microtubule cytoskeleton is attacked by multiple independent mechanisms—LIMK1 hyperactivation and cofilin inactivation (Ramsden), Ephexin5-RhoA-ROCK- mediated actin-myosin contraction (Margolis), competitive synaptic plasticity dysregulation (Huang), and microglial-mediated dendritic spine destruction (Shatz/Brott). The convergence of these mechanisms creates overdetermined, rapid structural collapse of synaptic connections. The Compensatory Paradigm Nexus (Chapter 10): Four frameworks (Moosmann, Rappoport, Ramsden, and Huang) independently converge on the concept that Aβ and/or tau serve compensatory, initially protective functions. The primary pathogenic insults (lipid peroxidation, excitatory insufficiency, allostatic overload, loss of Aβ monomer signaling) trigger compensatory responses that initially preserve neuronal function but eventually become pathologically overwhelming. The Neuroimmune Interface (Chapter 12): The microglial-complement pruning cascade (Shatz/Brott), mediated through C4d deposition and TREM2 signaling, integrates with neuronal immune recognition (pattern recognition through TLRs), oxidative stress signaling (ROS-mediated activation), and trans-synaptic immune signaling that triggers actin collapse from within the neuron. The neuroimmune response is both a consequence of neuronal pathology and an amplifier of that pathology. The ApoE4 Hub (Chapter 13): APOE4, a single structural polymorphism, simultaneously activates at least eight distinct pathogenic mechanisms across all six frameworks. APOE4 represents a master control point from which eight divergent pathogenic pathways emanate. The Transcriptional-Epigenetic Dysregulation Node (Chapter 14, partial): Multiple frameworks allude to dysregulation of gene expression, miRNA signaling, and epigenetic modifications. These changes both drive disease progression and are driven by the molecular perturbations at other nodes. These six nodes are not isolated; they are densely interconnected. The endosomal nexus drives the compensatory responses that characterize the compensatory paradigm nexus. The oxidative stress and calcium dysregulation at the endosomal nexus directly drive the actin cytoskeletal collapse that manifests at the cytoskeletal collapse node. The endosomal accumulation of DAMPS triggers the microglial-complement responses that constitute the neuroimmune interface. All three of these mechanisms are amplified by the APOE4 hub. The transcriptional dysregulation that results from perturbations at the other nodes feeds back to alter the expression of proteins at all nodes, creating self-reinforcing loops. The density of interconnection means that the network exhibits characteristics of highly integrated dynamical systems. A perturbation at one node rapidly propagates through the network to affect other nodes. The system shows nonlinear behavior—small perturbations may be buffered and absorbed by compensatory mechanisms, while perturbations exceeding certain thresholds trigger cascading failures. The system also exhibits hysteresis—once pathology has developed to a certain degree, reversal becomes difficult even if the original perturbation is removed, because the network has been reconfigured and new pathogenic loops have become established. A Temporal Staging Model The network model predicts a characteristic temporal sequence of disease initiation and progression, though with individual variation based on genetic and environmental factors: Stage 1: Molecular Initiation (Years -30 to -15 relative to symptom onset) In Stage 1, the primary pathogenic

insult begins to accumulate. In APOE4 carriers, the primary insult may be lipid peroxidation of ApoE cargo (Ramsden mechanism), initiated by oxidative stress from aging, diet, environmental exposures, or subtle mitochondrial dysfunction. In non- APOE4 carriers, the primary insult might be excitatory insufficiency (Moosmann mechanism), allostatic stress accumulation (Rappoport mechanism), or loss of Aβ monomer signaling (Huang mechanism). Whichever mechanism is operative, the primary insult accumulates slowly. At this stage, there is no histopathological evidence of disease—no plaques, no tangles, no neuroinflammation—yet the biochemical changes are initiating. The cell responds to the primary insult through the compensatory responses described in Chapter 10. If the primary insult is lipid peroxidation, the cell upregulates endogenous antioxidants, including monomeric Aβ (Ramsden). If the primary insult is excitatory insufficiency, the cell upregulates Aβ production and modulation of NMDA receptor trafficking to restore excitatory tone (Moosmann). If the primary insult is loss of Aβ monomer signaling, the cell attempts to increase Aβ production, attempting to restore the monomer concentration (Huang). These compensatory responses are adaptive—they partially mitigate the effects of the primary insult and maintain neuronal function. Stage 2: Endosomal Dysregulation and Compensatory Failure (Years -15 to -5) As the primary insult persists and accumulates, the compensatory responses themselves become dysregulated. Aβ production, initially adaptive, becomes excessive. The increased Aβ begins to accumulate in the endosomal-MVB system (Gouras). Retromer dysfunction may begin to manifest, either through primary genetic or environmental causation (Small) or as a secondary consequence of the accumulated Aβ and oxidative stress interfering with retromer assembly and function. The early endosome begins to accumulate Aβ, βCTF, and altered lipid species. The v-ATPase becomes impaired by lipid peroxidation (Ramsden). At this stage, the first signs of pathology may become apparent. Brain imaging might begin to show evidence of amyloid accumulation—in PET imaging, amyloid positivity emerges. However, cognitive function remains intact. The individual is asymptomatic but pathologically abnormal. This stage corresponds to the asymptomatic amyloid-positive state identified by recent longitudinal studies. Stage 3: Endosomal Nexus Consolidation and Cytoskeletal Perturbation (Years -5 to 0) The endosomal nexus becomes fully established. Lipid peroxidation is severe; ApoE is extensively oxidized and crosslinked to ApoER2 (Ramsden). Retromer dysfunction is pronounced; the early endosome is a traffic jam of APP, BACE1, βCTF, and cargo proteins (Small). Intraneuronal Aβ42 accumulates in MVBs (Gouras). The consequence is disruption of the Reelin- ApoER2-Dab1 pathway, with loss of suppression of GSK3β. GSK3β becomes hyperactive. GSK3β hyperactivation leads to widespread Tau hyperphosphorylation and to inactivation of SSH phosphatases, leading to LIMK1 hyperactivation and cofilin inactivation (Ramsden). Simultaneously, oxidative stress and calcium dysregulation drive Ephexin5-RhoA-ROCK pathway activation (Margolis), leading to actin-myosin contraction and dendritic spine collapse. The cytoskeletal collapse begins. By the end of this stage, the first dendritic spines have been lost, and early cognitive changes may become apparent. This stage corresponds to the transition from asymptomatic to mildly symptomatic cognitive impairment. Stage 4: Neuroimmune Activation and Synaptic Elimination (Years 0 to 5) As endosomal pathology

propagates and the first synapses are lost, the neuroimmune system becomes activated. Intraneuronal Aβ42, accumulating in MVBs, acts as a DAMP. Oxidatively modified proteins and hyperphosphorylated tau similarly activate pattern recognition receptors on microglia and astrocytes. The complement cascade is initiated (Shatz/Brott). C4d is deposited on synapses. Microglial CR3 and TREM2 recognize the C4d and engage with the marked synapses. Microglia-mediated phagocytosis of synapses increases dramatically. Simultaneously, the competitive synaptic plasticity mechanism described by Huang becomes fully activated. Synapses that have lost function due to actin collapse are unable to recover through normal plasticity mechanisms. Active synapses engage in increasingly intense competition for limited synaptic resources. The net result is progressive, accelerating synaptic loss. Dendritic spine density decreases precipitously. Cognitive decline accelerates. This stage corresponds to mild-to-moderate cognitive impairment. Stage 5: Network Disintegration and Advanced Pathology (Years 5 to 15) The progressive synaptic loss in Stage 4 continues to accelerate in Stage 5. Large networks of neurons lose their interconnections. The compensatory responses that were initiated in Stage 1 are fully exhausted; tau hyperphosphorylation is widespread, and neurofibrillary tangles form. Aβ plaques become prominent extracellularly, though they represent the end product of the intraneuronal pathology that began years earlier. Neuronal cell death becomes widespread. The stage-dependent spread of pathology through anatomically connected brain regions follows the Braak staging pattern. Pathology that initiates in the locus coeruleus and entorhinal cortex spreads to the hippocampus through anatomical connections and through trans-synaptic propagation of tau prions and Aβ oligomers. It progressively invades the neocortex. By the end of Stage 5, large regions of the cortex are dysfunctional or dead, and severe dementia is the inevitable consequence. This temporal staging model is hypothetical but generates testable predictions. It predicts that interventions applied in Stage 1 or Stage 2 should be far more effective than those applied in Stage 4 or Stage 5, because they could address the primary pathogenic insult before the networks of compensatory and pathological mechanisms are fully consolidated. It predicts that Stage 3—the transition from endosomal dysregulation to cytoskeletal collapse—should be a critical therapeutic window, as it represents the beginning of structural network destruction. It predicts that the asymptomatic amyloid-positive state (Stage 2) can persist for years or decades without cognitive symptoms because the synaptic structure is still largely intact, even though the molecular pathology is present.

Therapeutic Implications: The Network Perspective

The network architecture model suggests that monotherapeutic approaches —targeting a single pathogenic mechanism—are unlikely to succeed because of the redundancy and multi-layered nature of the network. If the network has consolidated such that multiple mechanisms are simultaneously active, blocking a single mechanism leaves the other mechanisms intact to drive pathology. However, the network model also suggests that carefully designed multi- target strategies

could have profound impact. A strategy that addresses the primary pathogenic insult (e.g., reducing lipid peroxidation, restoring excitatory tone, reducing allostatic load) while simultaneously supporting the compensatory responses and protecting against secondary cascade amplification (e.g., through antioxidant supplementation, NMDA modulation, and microglial modulation) could address multiple nodes simultaneously. Furthermore, the temporal staging model suggests that early intervention is paramount. An intervention applied in Stage 1 or early Stage 2, when the network is not yet consolidated and compensatory mechanisms are still functional, might succeed in preventing further progression. The same intervention applied in Stage 4 or Stage 5, when the network is deeply established and many neurons are dying, would be far less likely to succeed. The network model also identifies the critical points of vulnerability within the system. The endosomal nexus is a critical vulnerability because disruption at this point affects multiple downstream nodes simultaneously. APOE4, the master hub, is a vulnerability because it simultaneously affects eight distinct pathogenic mechanisms. The cytoskeletal collapse node is a vulnerability because the loss of synaptic connections represents the structural manifestation of disease and the basis of cognitive symptoms. The neuroimmune interface is a critical amplification point where compensatory-to-maladaptive transition in microglial function accelerates pathological progression. An advanced therapeutic strategy, informed by the network model, might prioritize intervention at these critical vulnerabilities:

1. Endosomal restoration: Restoration of v-ATPase function, restoration of retromer assembly, enhancement of lysosomal fusion and autophagy, reduction of endosomal PUFA peroxidation

2. APOE4-specific intervention: Restoration of disulfide bridge formation through chemical modification, restoration of protective lipid raft organization, modulation of lipid transport, reduction of complement activation

3. Cytoskeletal stabilization: Stabilization of dendritic spines through modulation of actin dynamics (e.g., LIMK1 inhibitors, RhoA inhibitors), enhancement of microtubule stability through tau-stabilizing mechanisms, support of synaptic adhesion

4. Compensatory support: Enhancement of endogenous antioxidant systems, restoration of excitatory tone through NMDA modulation, promotion of neuroplasticity through exercise and cognitive engagement

5. Immune modulation: Restriction of microglial activation to prevent excessive synaptic elimination, modulation of complement activation to prevent excessive C4d deposition while maintaining beneficial immune clearance, promotion of microglial phenotypes that support neuronal survival A therapeutic strategy incorporating interventions at all five levels would be complex and would need to be individually tailored to the patient's primary pathogenic driver and stage of disease. However, the network model suggests that only such a comprehensive approach stands a realistic chance of arresting or reversing disease progression. Network-Level Summary: The

Convergence Matrix The eight frameworks can be summarized in a convergence matrix that illustrates the degree to which each framework addresses each of the major pathogenic nodes: Table 4: Framework Convergence Matrix

Framework Endosomal

Nexus Cytoskeletal Collapse Compensato ry Paradigm Neuroimmun e Interface APOE4 Hub Transcriptio nal Dysregulatio n Ramsden Primary (lipid peroxidation, ApoER2- Primary (GSK3β, LIMK1, cofilin, Primary (Aβ as antioxidant) Secondary (oxidized lipids as Primary (disulfide bridge) Secondary (mentioned) Dab1, v- ATPase) tau phosphorylati on) DAMPs) Small Primary (retromer, SORL1, traffic jam) Secondary (lipid raft changes) Secondary (Aβ sequestration) Secondary (altered endosomal trafficking) Secondary (impaired retromer function) Not addressed Gouras Primary (intraneuronal Aβ42, MVBs, ESCRT) Secondary (loss of intraneuronal Aβ monomer signaling) Secondary (Aβ42 as compensatory or toxic?) Secondary (Aβ42 as DAMP) Secondary (enhanced intraneuronal Aβ42) Not addressed Moosmann Secondary (endosomal effects of NMDA hypofunction) Secondary (calcium dysregulation, CaMKII activation) Primary (NMDA hypofunction, compensatory Aβ/tau) Secondary (neuroinflam mation as secondary amplifier) Secondary (APOE4 reduces excitatory tone) Primary (CREB- mediated transcriptional changes) Rappoport Secondary (lipid raft effects on endosomal trafficking) Secondary (stress- induced cytoskeletal changes) Primary (allostatic load, adaptive-to- maladaptive transition) Secondary (neuroinflam mation as allostatic response) Primary (lipid raft organization, allostatic stress vulnerability) Primary (epigenetic changes, HDAC6) Margolis Secondary (endosomal activation of signaling cascades) Primary (Ephexin5- RhoA-ROCK, actin-myosin contraction, spine collapse) Not directly addressed Secondary (inflammatory signals as RhoA triggers) Secondary (APOE4 promotes Ephexin5- RhoA activation) Not addressed Huang Primary (APP processing, endosomal Aβ generation) Primary (competitive plasticity dysregulation, synaptic loss) Primary (Aβ monomer as synaptic signal, monomer depletion) Secondary (TNF/IL-1 effects on plasticity) Secondary (altered APP processing) Secondary (mentioned) Shatz/Brott Secondary (endosomal trafficking of complement) Primary (C4d- mediated synaptic pruning, trans-synaptic RhoA, spine elimination) Not directly addressed Primary (C4d- LilrB2- complement- TREM2- microglia pruning cascade) Secondary (altered complement activation) Not addressed Interpretation of the convergence matrix reveals that:

1. No single framework is comprehensive: Each framework addresses multiple nodes but not all. Ramsden is strong on endosomal and cytoskeletal mechanisms but weaker on neuroimmune aspects. Shatz/Brott is strong on neuroimmune and cytoskeletal mechanisms but addresses compensatory paradigm only implicitly.

2. The endosomal nexus has strongest support: Ramsden, Small, Gouras, and Huang all address it as either primary or secondary. This suggests that endosomal dysfunction is indeed a

central feature of disease.

3. Cytoskeletal collapse is highly convergent: Ramsden, Margolis, Huang, and Shatz/Brott all address it. This suggests that the loss of synaptic structure is not incidental to disease but rather central to it.

4. The compensatory paradigm is supported primarily by Moosmann and Rappoport: These two frameworks most explicitly articulate the concept that Aβ and tau are compensatory responses. The other frameworks implicitly acknowledge compensatory aspects.

5. APOE4 is a cross-cutting hub: All frameworks address APOE4 effects in at least secondary fashion, confirming that APOE4 is a critical control point with far-reaching effects.

6. Transcriptional dysregulation is under-addressed: Only Moosmann and Rappoport explicitly address transcriptional and epigenetic changes. This suggests that the integration of Alzheimer's disease with broader systems biology, including gene expression and epigenetic modifications, remains incomplete. The Unified Finding: Disease as Network Failure The central finding of this synthesis is that Alzheimer's disease is not a disease of a single pathogenic agent or mechanism. It is a disease of network failure—a progressive, cascading failure of multiple interdependent mechanisms, no single one of which is sufficient to cause disease, but whose convergent, synergistic operation produces inexorable neuronal and cognitive collapse. The eight frameworks, examined individually, each provide important but incomplete insights into pathogenesis. Viewed together, as an interconnected network, they reveal an elegant but terrible architecture: a system in which oxidative stress, endosomal dysfunction, receptor dysregulation, compensatory imbalance, cytoskeletal collapse, and immune- mediated destruction operate in feedback loops that progressively lock the system into a pathological state. No amount of anti-amyloid therapy, no degree of tau immunization, no simple intervention at a single node can be expected to reverse this network dysfunction. However, the network architecture also reveals hope. A clear, science-informed intervention strategy that addresses the primary pathogenic insult in its early stages, while simultaneously supporting compensatory mechanisms and preventing cascade amplification, has a realistic chance of arresting or reversing disease. The frameworks point toward targets— endosomal function, PUFA peroxidation, excitatory tone, lipid raft organization, dendritic spine stability, microglial phenotype—where multifaceted intervention could restore network homeostasis. The field now possesses, through these eight frameworks and their synthesis, a roadmap of sufficient detail and internal consistency to guide the next generation of therapeutic development. The task ahead is to translate this theoretical understanding into practical interventions that can be tested, refined, and ultimately deployed to combat one of humanity's most devastating diseases. --- Scientist Review Note This unified thesis synthesizing eight contemporary frameworks for Alzheimer's disease pathogenesis has been prepared under the Organic Network Synthesis (ONS) methodology by the AdultCognitiveDisease.com research initiative, under the oversight of Dr. James Truchard

and Benjamin Gustafsson. The synthesis represents analytical interpretation and integration of the theoretical and empirical content presented in the original frameworks authored by Christopher Ramsden, Steven Small, Gunnar Gouras, Bernd Moosmann, Ari Rappoport, Seth Margolis, Zhen Huang, and Carla Shatz and Barbara Brott. The purpose of this synthesis is to make available to the scientific and clinical communities a comprehensive mapping of how eight independently developed pathogenic models for Alzheimer's disease interconnect, converge, and integrate into a unified network architecture. The authors have attempted to preserve the specific claims, mechanisms, and emphasis of each original framework while identifying the points of convergence, complementarity, and genuine tension that emerge when the frameworks are examined as an integrated whole. This synthesis is offered for review by the original investigators whose work is evaluated. We welcome correction, clarification, and amendment from the original authors. Where the synthesis may have misinterpreted or misrepresented their work, we invite detailed feedback so that future iterations can reflect the intended meaning of the original frameworks more accurately. The current synthesis is viewed as provisional and subject to refinement through scientific dialogue. The frameworks and the synthesis are made available with the recognition that Alzheimer's disease research has historically been dominated by a single hypothesis—the amyloid cascade—for over three decades. This synthesis does not argue for the abandonment of amyloid biology, which clearly has relevance. Rather, it argues for its integration into a broader network of mechanistic understanding that encompasses lipid peroxidation, endosomal trafficking, receptor signaling, kinase dysregulation, cytoskeletal dynamics, synaptic plasticity, and immune function. The frameworks presented and synthesized here represent a genuine departure from the amyloid-dominated paradigm toward a more inclusive, network-level understanding of disease. We hope this synthesis serves the broader goal of accelerating the translation of mechanistic understanding into effective therapeutic intervention for patients affected by Alzheimer's disease. Unified Works Cited This unified bibliography consolidates all 398 unique references cited across the eight source theses. References appearing in multiple theses are noted. 1. 16th Clinical Trials on Alzheimer's Disease (CTAD), accessed March 23, 2026, https://www.ctad-alzheimer.com/files/files/CTAD%20ABSTRACT%202023%20%28V2%29.pdf 2. 2022 BrightFocus Foundation Alzheimer's Disease Research Projects, accessed March 23, 2026, https://www.brightfocus.org/wp-content/uploads/2025/01/2022-ADR-Yearbook- WCAG-2023.pdf 3. 2025 Alzheimer's disease facts and figures - PMC - NIH, accessed March 30, 2026, https://pmc.ncbi.nlm.nih.gov/articles/PMC12040760/ 4. 8: Oskar Fischer (1876-1942) was both a pioneering and tragic figure in... - ResearchGate, accessed March 23, 2026, https://www.researchgate.net/figure/Oskar- Fischer-1876-1942-was-both-a-pioneering-and-tragic-figure-in-the-history- of_fig8_258334262

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