
The Persistent Alarm

cGAS–STING, DNA Surveillance, and Synaptic Resilience in Alzheimer’s Disease

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From the discoveries of Zhijian (James) Chen and colleagues to the cellular mechanisms that sustain inflammation and impair synaptic resilience.

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Abstract

The cGAS–STING pathway supplies a molecular connection between misplaced DNA and inflammatory signalling. Its relevance to Alzheimer’s disease extends from mitochondrial and genomic damage to microglial state, neuronal resilience, and the fate of activated signalling proteins. The discoveries of Zhijian (James) Chen and colleagues at UT Southwestern Medical Center established cGAS as a DNA-activated enzyme and cGAMP as the second messenger linking DNA recognition to STING. Subsequent work has shown that the consequences of this system depend on DNA accessibility, membrane composition, cellular location, signal duration, and the responding cell. These variables make cGAS–STING a useful framework for investigating how a normally protective response becomes persistent and injurious.

This critical review develops three propositions. First, DNA sensing can translate several forms of cellular damage into a shared inflammatory response without establishing a single initiating cause of Alzheimer’s disease. Second, neuronal and microglial responses must be distinguished: interferon-associated suppression of neuronal MEF2C, complement-associated synapse removal, and TNF-dependent neurotoxicity are different experimental outcomes. Third, STING activation and STING termination are separately regulated. Lysosomal dysfunction can increase DNA-dependent activation, delay the removal of activated STING, or interfere with protective STING-associated repair functions. A uniform instruction to increase clearance or suppress all STING activity therefore lacks sufficient mechanistic resolution.

The review integrates foundational biochemistry, structural studies, human genetic observations, and experimental ageing and disease models. Persistent injury can arise from continuing DNA or messenger input, retained STING signalling competence, or slowly resolving recipient-cell responses. Membrane lipids and organelle traffic regulate more than one of these processes, making their effects dependent on compartment and timing. A proposed connection from interferon to neuronal MHC-I and PirB/LILRB2 signalling is evaluated as a mediation hypothesis alongside established inflammatory pathways.

A staged experimental programme follows. It measures DNA production and removal, cGAMP, activated STING residence, cell-specific inflammatory responses, and surviving functional synapses. Pulse-and-withdrawal experiments separate continued initiation from defective termination; genetic and pharmacological bypass experiments establish pathway order. The central therapeutic question is which component remains necessary for ongoing injury after the initiating insult has occurred, and whether interrupting that component permits recovery of useful neuronal function.

I. DNA Surveillance and the Problem of Persistent Injury

1.1 From a molecular alarm to a circuit outcome

An inflammatory response can be appropriate when it begins and harmful when it persists. A cell that detects DNA in an abnormal setting may induce a protective programme even when the DNA originated within the organism. The significance of the response cannot be decided from the identity of the sensor alone. It depends on what became accessible, how long the signal lasts, which other cells receive it, and whether the tissue can recover when the initiating disturbance has ended.

Alzheimer's disease makes these distinctions unusually important because molecular pathology, cellular dysfunction, synapse loss and cognitive impairment do not coincide perfectly in time or severity. Terry and colleagues' human neuropathological work established a strong relationship between synaptic measures and cognitive impairment. The observation gives the synapse a central place in a mechanistic account, while leaving open how particular immune, metabolic or proteostatic abnormalities damage it. A reduction in pathological material and preservation of a functioning circuit are related objectives whose equivalence has to be demonstrated.¹

cGAS-STING provides a means of connecting intracellular damage to a tissue response. It does not provide, by its existence, an explanation of every transition from ageing to dementia. The name joins an enzyme that generates a messenger to a membrane protein that receives and propagates that messenger. The full biological system includes DNA-binding competitors, nucleases, transport routes, kinase assemblies, cytokine receptors and removal mechanisms. Each creates a possible point of regulation and a potential source of disagreement between experiments.

The distinction between a pathway and a disease mechanism is the starting point of this paper. Establishing that a molecular reaction is possible differs from establishing that it occurs in the relevant human cells. Demonstrating that the reaction contributes to injury in a mouse differs from establishing that it remains necessary at the stage when a person could receive treatment. A useful synthesis must retain these differences while identifying experiments that connect them.

1.2 The intellectual contribution of the Chen programme

Zhijian (James) Chen's work is central because it converted an inflammatory response into a sequence of experimentally separable biochemical operations. The cGAS and cGAMP discoveries offered an enzyme, a product and a downstream receiver that could be isolated, reconstituted and perturbed. That architecture makes it possible to ask whether an apparent inflammatory phenotype begins with DNA sensing, messenger transport, membrane-dependent activation or a failure further downstream. The historical and molecular details are developed in Chapters 2–4.

The same logic should govern a synthesis of neurodegeneration. When several interventions reduce the same inflammatory marker, they need not act through the same mechanism. An intervention that prevents DNA from reaching cGAS, one that prevents cGAMP production, and one that shortens STING residence could converge on a transcriptional endpoint while having different consequences for neuronal repair. Conversely, a reduction in interferon may leave another STING-dependent output active. Biochemical dissection is valuable precisely because it prevents a shared readout from erasing these distinctions.

Attribution in this account follows the published work. Chen and collaborators made foundational contributions to cGAS and cGAMP, while the identification and characterisation of STING and the elucidation of its chemistry, structures and regulation involved several laboratories. The paper treats discovery as a cumulative experimental programme. Chen's role is presented through the questions his work made answerable and the mechanisms his group helped establish, including new membrane-lipid findings in 2026.

1.3 Three questions that organize the review

The first question is **initiation**: what material becomes accessible to the sensing machinery? A mitochondrial lesion, a damaged nuclear boundary and a derepressed retroelement can produce different molecular substrates and time courses. Their ability to converge on an immune pathway does not make them interchangeable causes. The relevant experiment must identify the DNA species, its location and the change that made it available.

The second question is **propagation**: how does the response move between compartments and cells? A neuron may be the source of a damaging material, a microglial cell may sense it, and another neuron may lose a transcriptional programme that supports resilience. A whole-tissue average combines these roles. Disentangling them is necessary to interpret both protective genotypes and cell-targeted interventions.

The third question is **termination**: what must happen for the response to end? Removing an extracellular stimulus does not necessarily remove intracellular DNA. Degrading DNA does not instantly erase cGAMP, activated STING, secreted cytokines or transcriptional consequences. A

tissue can therefore remain altered after one upstream measurement has returned to baseline. Persistence has to be located experimentally rather than inferred from a late endpoint.

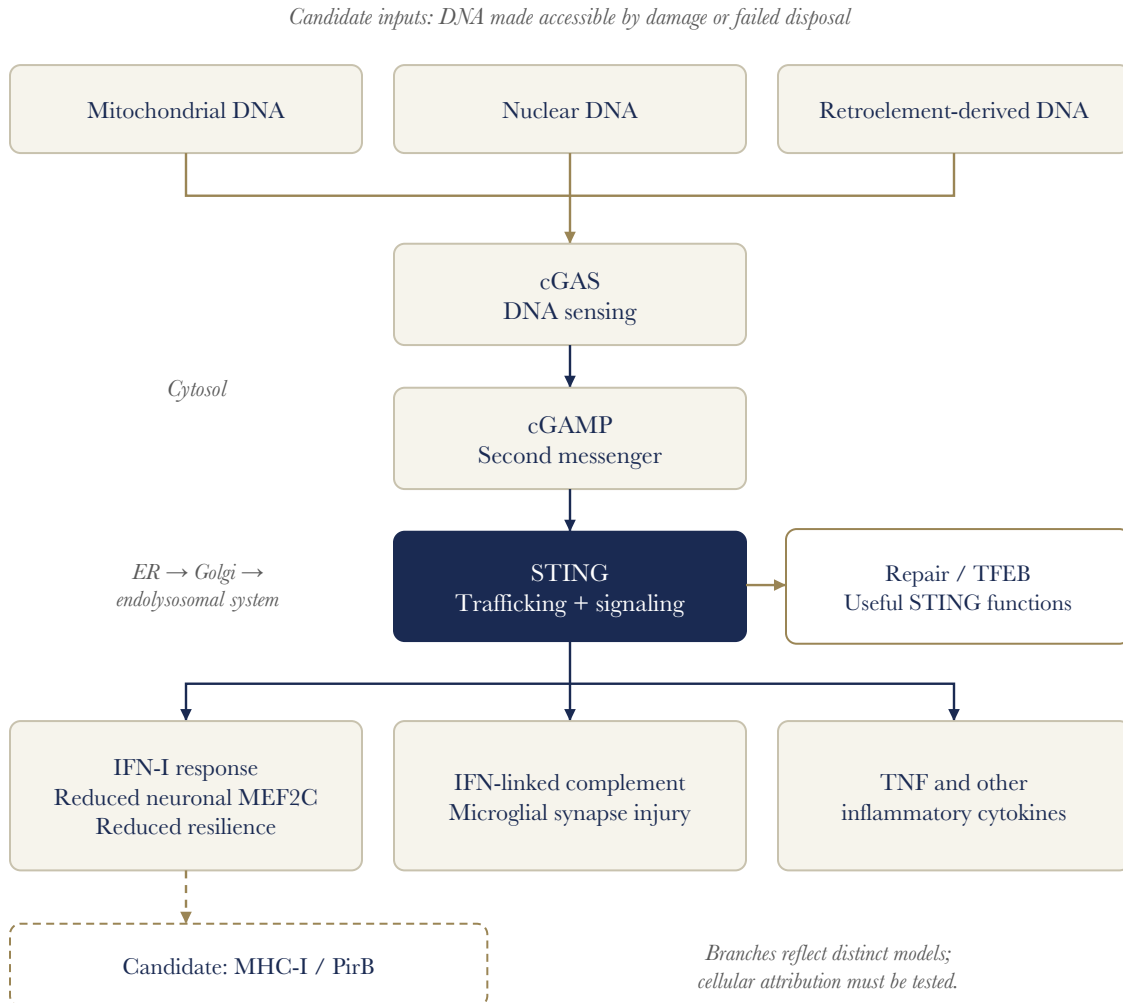


Figure 1. Distinct models connect DNA sensing to neuronal, microglial, and cytokine responses. These branches are not one universal cascade. The IFN/complement branch has other possible upstream sensors. Dashed IFN-I to MHC-I/PirB mediation remains untested; STING also has repair functions. Sources: ^{63, 61, 70, 96}.

1.4 Evidence scope and terminology

This is a critical mechanistic review and experimental synthesis, not a systematic meta-analysis or a report of new biological data. It considers primary literature available through 10 September 2026, with emphasis on studies that alter the interpretation of causality, cell type or signal termination. Human observational findings, genetic evidence, cellular perturbations and animal experiments are identified by their experimental scope. Proposed integrations and mathematical descriptions are labelled as such.

The term cGAS refers to cyclic GMP–AMP synthase; CGAS is the current human gene symbol, and MB21D1 is a historical alias. STING refers to the protein encoded by STING1, historically TMEM173. Type I interferon is abbreviated IFN-I, and its receptor is IFNAR. These names should not be treated as synonyms for generic innate immunity. RNA-sensing receptors, inflammasomes and other pathways can generate overlapping downstream states while retaining distinct inputs and dependencies.^{2, 3}

“Resilience” denotes retained function in the presence of a specified challenge or pathology. It does not imply that the challenge is harmless or that every pathological measurement remains unchanged. “Termination” denotes decline of a defined signal after its source is removed or controlled. “Clearance” denotes removal of a specified material from a specified compartment; uptake alone does not establish digestion. These operational definitions permit direct comparison of apparently similar observations.

2. Chen’s Biochemical Programme and the Discovery of a DNA Alarm

2.1 Attribution and the scope of the contribution

Zhijian (James) Chen, PhD, is a professor of molecular biology at UT Southwestern Medical Center, where he holds the George L. MacGregor Distinguished Chair in Biomedical Science. His laboratory’s work made innate immune signalling accessible to biochemical reconstruction. This paper follows that experimental programme from the recognition of a cytosolic DNA response to the isolation of its enzyme, messenger and molecular control mechanisms.^{4, 5}

Chen and colleagues’ identification of cGAS and cGAMP gave the field a mechanistic connection between exposed DNA and an already recognized inflammatory signalling apparatus. The advance was unusually useful because it separated a DNA-responsive enzyme, its diffusible

product, and the product's receptor. That separation allows different parts of the response to be measured and interrupted independently. In this review, the resulting experimental logic matters as much as the historical sequence: an interferon response becomes a phenomenon whose initiating substrate, catalytic step, and downstream relay can be tested.^{6, 7}

The discovery should nevertheless be attributed at the level of particular claims. Identifying a protein, demonstrating an immune function, discovering its ligand, resolving ligand chemistry, and establishing relevance in an organism are distinct contributions. A narrative that credits one laboratory with the complete modern pathway would erase work necessary to interpret it accurately. The following account therefore distinguishes Chen's central cGAS–cGAMP discovery from the earlier identification of STING and the parallel structural and chemical studies that followed.

2.2 RNA sensing as a methodological precedent

In 2005, Seth, Sun, Ea and Chen identified MAVS as a mitochondrial antiviral signalling protein required for activation of NF- κ B and IRF3 following viral infection. This work placed a signalling adaptor on a defined organelle and connected it functionally to an antiviral response. MAVS belongs to the RNA-sensing RIG-I-like receptor system, not to the catalytic cGAS DNA-sensing reaction. Its relevance here is that immune signalling could be understood through the physical organization of its components, rather than only through the eventual transcriptional response.⁸

Hou and colleagues subsequently demonstrated that activated MAVS can form large, functional assemblies with prion-like propagation properties. Recombinant fibrillar material could promote conversion of endogenous MAVS into a signalling-active state, providing a biochemical explanation for amplification. This was a study of physiological antiviral signal assembly, not a demonstration that MAVS causes a transmissible protein disease. Nor does it establish that cGAS condensates, STING oligomers, amyloid- β , and tau share one pathogenic assembly mechanism.⁹

The useful continuity is an emphasis on how a small initiating event becomes a substantial response. A signalling pathway can acquire gain through catalysis, cooperative assembly, or communication between cells, and those mechanisms need not have identical persistence. The present review therefore uses the MAVS work as methodological context without importing its prion-like terminology into every cGAS–STING process. Describing the physical step that amplifies a signal is more informative than describing all sustained inflammation as an aggregate-driven phenomenon.

2.3 STING preceded the identification of cGAS

In 2008, Ishikawa and Barber identified STING through expression cloning and showed that it facilitated innate immune signalling. Their experiments linked the membrane-associated protein to IRF3 and NF- κ B activation and interferon production. The same year, Zhong and colleagues identified the adaptor MITA in virus-induced IRF3 signalling. These studies established functions of the protein subsequently integrated into the cGAS pathway, although aspects of its localisation and upstream relationships continued to be refined.^{10, 11}

Lei Jin and colleagues had earlier described the same protein as MPYS in a study of a membrane tetraspanner associated with major histocompatibility complex class II and apoptotic signalling. An explicit correction to the Ishikawa–Barber article acknowledged that STING and the previously described MPYS were encoded by the same gene. This is an important attribution boundary: discovery of the protein and discovery of its DNA-related immune role are related but distinguishable events. The original MHC-II observation should also not be mistaken for evidence connecting cGAS to neuronal MHC-I–PirB signalling.^{12, 13}

Burdette and colleagues added a decisive ligand-level result in 2011 by showing that STING directly binds the bacterial cyclic dinucleotide c-di-GMP. Their experiments distinguished recognition of cyclic dinucleotides from the cellular response to DNA. Thus, before cGAS was identified, STING was already understood to combine an adaptor role with direct recognition of a small nucleotide signal. This provided part of the intellectual setting in which a mammalian DNA-induced messenger could explain communication between DNA and STING.¹⁴

2.4 The coupled discoveries of cGAMP and cGAS

Wu and colleagues identified cGAMP as an endogenous second messenger produced in response to cytosolic DNA and capable of activating STING. The contribution included Jiayi Wu, Lijun Sun, Xiang Chen, Fenghe Du, Heping Shi, Chuo Chen and Zhijian J. Chen. It established a chemical relay between an upstream DNA stimulus and a downstream immune response. The publication belongs to the 2013 Science issue, with online publication in December 2012; both dates can therefore appear in bibliographic records without referring to different discoveries.⁷

The companion work led by Lijun Sun used biochemical fractionation and quantitative mass spectrometry to identify the enzyme responsible for the activity. The resulting cGAMP synthase, cGAS, bound DNA and produced cGAMP, while loss-of-function experiments impaired DNA-triggered interferon signalling. The same article connected the biochemical activity to STING-dependent cellular responses. Together, the studies supplied an enzyme–product–receptor sequence that was substantially more specific than an association between DNA damage and inflammatory gene expression.⁶

For neurodegeneration research, this distinction creates a demanding standard of explanation. If cGAS is proposed to couple organelle injury to inflammatory signalling, the argument should identify evidence that the relevant DNA becomes available, that catalysis occurs, and that the downstream response depends on the expected relay. Increased expression of pathway components can guide that investigation but does not replace it. This is an analytical consequence of the discovery architecture, rather than a claim that the original papers studied Alzheimer's disease.

2.5 Parallel chemistry and an expanding framework

The messenger's exact structure was established through several complementary studies in 2013. Ablasser and colleagues demonstrated its noncanonical 2'-5' linkage; Gao and colleagues resolved the mixed-linkage product and a stepwise synthetic mechanism; Diner and colleagues distinguished the cGAS product from conventional bacterial cyclic dinucleotides in activation of human STING. Zhang and colleagues showed that endogenous 2'3'-cGAMP is a high-affinity STING ligand and examined the structural basis of recognition. These contributions should be cited together when assigning the unusual bond chemistry, rather than treating the chemical refinement as a single unshared event.^{15, 16, 17, 18}

The framework remains open to experimentally established additions. A 2026 study by Tan and colleagues identified phosphatidylinositol 3,5-bisphosphate as an endogenous STING ligand associated with the PIKfyve regulatory system; a companion structural study examined phosphoinositide and cholesterol contributions to STING activation. These results extend the importance of membrane composition without replacing the cGAMP relay described above. Their detailed implications for signalling compartments and disposal are considered later in this review, with the same distinction between biochemical demonstration and disease-specific inference.^{19, 20}



Figure 2. Selected discoveries and their attribution. *STING* discovery involved Barber's laboratory and other teams; the later *cGAS/cGAMP*, condensate, and lipid findings include Chen and collaborators. This is a selective timeline. Sources: ^{8, 10, 6, 7, 27, 19, 20}.

3. DNA Recognition, Messenger Chemistry and Amplification

3.1 DNA is the activating ligand, not the nucleotide substrate

The cGAS reaction should be described with three different molecular roles. Double-stranded DNA promotes activation of the enzyme; ATP and GTP supply the nucleotides; 2'3'-cGAMP is the product that communicates with STING. DNA is therefore not incorporated into cGAMP and is not consumed as the enzyme's nucleotide substrate. This distinction prevents a misleading interpretation in which every measured DNA fragment corresponds to one unit of messenger production.¹⁶

Structures reported by Civril and colleagues showed how DNA binding produces an activating conformational change in cGAS. A distinctive zinc-containing structural element helps the enzyme recognize double-stranded DNA, while the catalytic core becomes competent for dinucleotide synthesis. Kranzusch and colleagues independently resolved human cGAS and established structural relationships to the RNA-responsive oligoadenylate synthetase family. The shared nucleotidyltransferase scaffold makes second-messenger production a central part of recognition, while divergent structural features help determine which nucleic acid activates the enzyme.^{21, 22}

The consequence for interpretation is that DNA binding, catalytic competence, and product accumulation should be treated separately. A protein can remain physically associated with DNA while adopting a state that does not produce much messenger. Conversely, an activated enzyme can repeatedly generate product while a stimulating DNA molecule persists. In the persistent-alarm hypothesis developed in this paper, DNA availability and messenger generation are therefore related variables with different kinetics, rather than interchangeable biomarkers.

3.2 The two linkages specify a chemically distinct message

Mammalian 2'3'-cGAMP contains one phosphodiester bond involving the 2' position of the guanosine ribose and another involving the 3' position of the adenosine ribose. This mixed connectivity distinguishes it from cyclic dinucleotides with two conventional 3'-5' linkages. Ablasser and colleagues' chemical work established the noncanonical linkage, and Diner and colleagues showed why distinguishing the endogenous product from bacterial-type molecules mattered for human STING responses. The abbreviated term cGAMP should consequently be expanded to 2'3'-cGAMP when chemical identity affects the inference.^{15, 17}

Gao and colleagues found that synthesis proceeds through a linear intermediate before ring closure, connecting the enzyme's conformational state to the final bond arrangement. Zhang and colleagues then demonstrated high-affinity recognition of the mixed-linkage product by STING. These findings show that the pathway does not merely respond to an undifferentiated increase in cyclic nucleotides. It transmits a structurally specified signal whose formation and recognition can each be perturbed.^{16, 18}

This chemistry has a practical implication for experimental controls. A synthetic cyclic dinucleotide can test downstream responsiveness only to the extent that its cellular delivery and receptor activity are understood. A response to an artificial STING agonist does not establish that endogenous cGAS was active before treatment. Conversely, failure to respond may reflect delivery or receptor properties rather than the absence of a DNA-sensing apparatus; a meaningful experiment must identify which step the reagent actually interrogates.

3.3 Cooperative recognition makes DNA architecture consequential

Li and colleagues resolved a complex in which cGAS engages double-stranded DNA through two binding surfaces and assembles into a 2:2 enzyme–DNA arrangement. Mutating DNA-interaction or dimer-interface residues impaired activity, linking the architecture to function. This established that recognition involves cooperative organization of molecules, rather than only a solitary enzyme touching an arbitrary piece of DNA. It also explained why mutations outside the catalytic pocket can substantially alter cGAMP production.²³

Luecke and colleagues demonstrated that DNA length influences cGAS activity, particularly at low DNA concentrations. Recombinant human cGAS showed this behaviour without requiring a cellular accessory factor, and the relationship extended over a broad range of DNA lengths. The study argues against treating DNA mass alone as a sufficient description of an immunostimulatory preparation. It does not establish one universal minimum length applicable to every species, concentration, protein construct, or intracellular environment.²⁴

Andreeva and colleagues supplied a structural explanation through ladder-like cGAS–DNA assemblies. Once an initiating cGAS dimer organizes neighboring DNA segments, subsequent binding becomes more favorable; DNA-bending proteins including HMGB1 and TFAM can help organize permissive substrates. This adds geometry and protein packaging to the relevant description of DNA. In considering mitochondrial DNA, the meaningful question is therefore not simply whether it is present outside mitochondria, but also how it is organized and accessible to the sensing machinery.²⁵

3.4 Human and mouse cGAS are not interchangeable reagents

Zhou and colleagues demonstrated that human cGAS has enhanced DNA-length discrimination associated with specific substitutions in its DNA-binding surface. Structural and functional experiments showed how these substitutions alter formation of a minimally active complex while preserving stronger responses to longer DNA. The study also identified active-site features relevant to species-specific inhibitor sensitivity. Mouse biochemical activity therefore cannot be assumed to supply the quantitative activation threshold or pharmacological response of the human enzyme.²⁶

This distinction matters when connecting animal results to human microglia or neurons. A mouse model may convincingly demonstrate that a pathway can contribute to a phenotype while leaving unresolved the stimulus strength required in a human cell. Similarly, a compound that suppresses a mouse experiment may require separate evidence of human enzyme engagement. Translational confidence improves when the same causal ordering is reproduced across species with appropriate reagents, even if the absolute response sizes differ.

Cross-species comparison should consequently preserve the distinction between conservation and equivalence. Conservation means that corresponding molecular components can execute a related reaction; equivalence would require matching behaviour under the conditions relevant to the question. For this review, the principal claim of interest is conservation of a potentially damaging signal relay, followed by direct testing of human thresholds and outputs. A universal numerical rule for DNA length or inhibitor potency would imply more than the structural evidence supports.

3.5 Condensation can alter both response strength and stimulus lifetime

Du and Chen showed that DNA can induce liquid-like condensation of cGAS and that the enzyme is active within the resulting assemblies. The positively charged, disordered N-terminal region increased multivalent interactions, and longer DNA more effectively promoted condensation and activity. These experiments connected a physical transition in a protein–DNA system to messenger production. They provide a mechanistic reason to consider local organization when bulk concentrations appear insufficient to explain a response.²⁷

Subsequent work by Zhou, Mohr, Maciejowski and Kranzusch separated condensation from catalysis more sharply. Their results indicated that cGAS–DNA phase separation can protect the DNA stimulus against TREX1-mediated degradation, with nuclease activity restricted by the condensate environment. Thus, a condensate can support sensing through control of stimulus lifetime even where condensation itself is not the immediate determinant of catalytic output. The two studies motivate distinct questions about productive enzyme organization and resistance to negative regulation.²⁸

A visible cGAS punctum is therefore an incomplete explanation. It does not, by morphology alone, identify a liquid material state, establish cGAMP synthesis, or demonstrate pathological persistence. The proposed interpretation of a cellular assembly should fit measurements of its dynamics and biochemical activity. In an Alzheimer's disease model, prolonged puncta could be compatible with continued DNA exposure, delayed disassembly, or altered degradation; discriminating among those possibilities is part of establishing the mechanism rather than an optional descriptive refinement.

3.6 Amplification and persistence require different explanations

The pathway contains several opportunities for amplification, but amplification is not synonymous with persistence. Catalysis permits an activated enzyme to produce repeated messenger molecules, cooperative DNA interactions can sharpen a response to substrate, and downstream cellular communication can extend the territory affected. Each mechanism explains how an initiating input acquires influence. None independently proves that signalling will continue after the input has disappeared.

This review uses persistence in a stricter operational sense: a response remains elevated because an activating input continues, a permissive state is maintained, or negative regulation fails to restore the baseline. These possibilities predict different relationships between DNA abundance, cGAMP, STING activation, and later transcription. They also differ in whether interrupting the initial sensor should rapidly reverse the phenotype. Treating the variables separately allows the persistent-alarm model to make discriminating predictions rather than functioning only as a metaphor for chronic inflammation.

The chemical and structural literature consequently supports a layered interpretation of pathway measurements. cGAS protein describes potential sensing capacity; accessible DNA describes a candidate ligand; cGAMP reports a product; downstream phosphorylation describes relay activity; and inflammatory transcription describes a later response. A persuasive causal argument orders those layers in time and tests their dependence. The value of the foundational discoveries is that this ordering is experimentally accessible, even where the disease model contains many additional feedback processes.

3.7 The messenger can cross cellular boundaries

cGAMP production and STING reception need not occur in the same cell. Ablasser and colleagues demonstrated transfer of cGAS-produced cGAMP through gap junctions in human and mouse cellular systems, with STING activation and antiviral protection in neighbouring cells independently of type I interferon signalling. This establishes a direct nucleotide-mediated relay alongside cytokine-mediated communication. For a tissue experiment, the inference is consequential: activated STING identifies a responding cell, but does not establish that this cell originally encountered the DNA or synthesized the messenger. A negative cGAS perturbation confined to the recipient therefore cannot exclude cGAS dependence in the source.²⁹

The messenger also has a regulated lifetime. Li and colleagues identified ENPP1-mediated 2'3'-cGAMP hydrolysis using biochemical purification, recombinant enzyme, and comparisons involving Enpp1-deficient mouse material. Their hydrolysis-resistant analog retained STING binding while producing stronger responses in the tested cellular assays, separating ligand recognition from ligand survival. These findings establish enzymatic destruction as a control on messenger availability; they do not make ENPP1 the universal cytosolic disposal mechanism. In a compartmental model, extracellular hydrolysis must be distinguished from loss of intracellular cGAMP, because the enzyme and substrate must encounter each other before degradation can shorten exposure.³⁰

Entry into a recipient is similarly conditional. Ritchie and colleagues identified the folate transporter SLC19A1 as a cGAMP importer through a genetic screen in human U937 cells, with supporting transport-related perturbations and preserved responses when cGAMP was introduced by electroporation. Dependence varied across human cell lines and primary monocyte donors, demonstrating that a strong result in one preparation does not establish universal transporter use. These human-cell experiments cannot assign the dominant route in mouse brain, human microglia or neurons. An extracellular cGAMP challenge therefore tests delivery and intracellular response together unless a bypass control establishes that STING remains competent when membrane entry is circumvented.³¹

Export can have a different effect in the producing cell. Maltbaek and colleagues identified ABCC1 as an ATP-dependent cGAMP exporter in mouse and human systems and supported direct transport with membrane-vesicle experiments. Increasing export restrained cell-intrinsic STING signalling, whereas ABCC1 deficiency aggravated cGAS-dependent disease in Trex1-deficient mice.³² Taken together, these studies imply that reducing the source-cell messenger pool can redistribute exposure rather than simply extinguish a tissue response. The proposed Alzheimer experiments should accordingly measure intracellular and extracellular cGAMP and distinguish source-cell cGAS from recipient-cell STING; none of these studies establishes a dominant cGAMP transporter or transfer route in Alzheimer's disease.

4. Self-Tolerance: Localization, Chromatin and DNA Accessibility

4.1 The cell must tolerate an abundance of its own DNA

A DNA-responsive enzyme creates a problem that cannot be solved by recognition chemistry alone: normal nucleated cells contain an enormous endogenous DNA reservoir. Because cGAS can respond to self-DNA under permissive conditions, preventing harmful activation requires regulation of encounters and productive assemblies. The question is not whether a healthy cell contains DNA, but why most DNA–protein encounters do not initiate an inflammatory response. Studies of localisation and chromatin tethering provide direct experimental answers to parts of this question.^{33, 34}

The familiar description of cGAS as exclusively cytosolic is inadequate. Volkman and colleagues found predominantly nuclear endogenous cGAS in their tested systems and identified a strong chromatin-dependent tether that restrained self-reactivity. Barnett and colleagues instead established an important plasma-membrane-associated pool in their macrophage-centred experiments, dependent on N-terminal phosphoinositide interactions. These results should be presented as evidence for regulated and context-sensitive positioning, rather than forcing all cells into one localisation rule.^{33, 34}

This matters for interpretation of tissue images. Nuclear cGAS staining does not by itself mean that a cell is experiencing an inflammatory DNA response, while an apparently cytoplasmic pool may be heterogeneous in accessibility and activity. Localization supplies information about where a mechanism could occur; the catalytic state still needs evidence. In brain tissue, the relevant cellular identity and physiological condition should therefore accompany any claim that redistribution marks a disease-associated failure of self-tolerance.

4.2 Chromatin is an inhibitory binding environment

The nucleosome studies gave nuclear restraint a molecular explanation. Zhao and colleagues showed that cGAS binds a negatively charged surface formed by histones H2A and H2B, with high-affinity interactions that inhibit productive DNA sensing. Mutations that weakened the interaction increased cellular cGAMP production, connecting the structural interface to function. Chromatin therefore contributes active inhibition rather than serving solely as a physical container that keeps DNA away from an enzyme.³⁵

Boyer and colleagues independently resolved a cGAS–nucleosome complex and identified conserved arginine anchors engaging the nucleosomal acidic patch. The arrangement occupies a major DNA-interaction surface and prevents formation of the productive oligomeric state. This demonstrates why DNA binding can coexist with catalytic restraint: the geometry of the encounter differs from the geometry that activates the enzyme. It also explains why a localisation assay alone cannot distinguish an inhibited nuclear complex from an inflammatory signalling event.³⁶

The distinction is useful when interpreting experiments that disrupt chromatin binding. A constitutively active tethering mutant tests the consequences of removing a restraint, not necessarily the natural mechanism by which that restraint fails during ageing. Its phenotype can establish that a normally suppressed pool has signalling potential. To assign the same mechanism to sporadic disease, evidence would be needed that the corresponding interface, occupancy, or chromatin context changes under the disease condition.

4.3 Competition protects DNA when compartment boundaries fail

Barrier-to-autointegration factor 1, usually abbreviated BAF, supplies another form of restraint. Guey and colleagues showed that BAF dynamically competes with cGAS for genomic DNA binding and limits immune activation when nuclear membrane integrity is acutely compromised. The protective mechanism operates even after the simple spatial separation of nucleus and cytoplasm has failed. It therefore establishes that exposed nuclear DNA is not automatically equivalent to a productive cGAS stimulus.³⁷

An independent study by Ma and colleagues linked BAF1 to suppression of a basal cGAS–STING response. Together, the studies support the broader principle that DNA-binding competitors help regulate innate immune thresholds. The principle should not be expanded into a claim that BAF loss is an established cause of Alzheimer’s disease or a universal explanation for age-related interferon signalling. Its relevance here is mechanistic: accessibility can be controlled by competition as well as by membrane integrity.³⁸

This produces a more informative interpretation of nuclear damage. A damaged boundary may expose potential substrate, but the resulting response will depend on the availability and state of competing DNA-binding factors. The same gross lesion could therefore yield different signalling outcomes in different cells or at different times. A disease-associated increase in DNA exposure should be evaluated alongside the regulatory context that determines whether the exposed material becomes a sustained stimulus.

4.4 Mitosis demonstrates layered restraint, with limited neuronal extrapolation

Mitosis presents a physiological challenge because nuclear-envelope breakdown exposes chromatin to proteins that were previously separated from it. Li and colleagues demonstrated that cGAS is suppressed during mitosis through parallel mechanisms: inhibitory N-terminal phosphorylation and chromatin tethering that prevents productive oligomerization. Their biochemical analysis distinguished these restraints rather than assigning inhibition to a single cause. The work shows that a cell can maintain tolerance during substantial changes in subcellular organization.³⁹

The same study found differing requirements of the cGAS N-terminal region for sensing nuclear chromatin and mitochondrial DNA. That result cautions against assuming that all endogenous DNA sources are regulated identically. An intervention that changes recognition of nuclear chromatin may have a different effect on mitochondrial DNA sensing. The origin of a stimulus therefore carries mechanistic information beyond simply classifying it as self-DNA.³⁹

Mature neurons are generally not dividing, so mitotic suppression cannot be imported wholesale as an explanation of neuronal resilience. The direct application of these experiments is stronger for understanding dividing cells and the design of cGAS regulation than for assigning a neuronal disease mechanism. Nevertheless, the layered organization is conceptually relevant: removal of one restraint may leave another functioning. This is a reason to test combinations of regulatory failures carefully, without treating the existence of multiple controls as evidence that they all fail in Alzheimer's disease.

4.5 DNA degradation competes with protected signalling assemblies

Stimulus disposal is another part of self-tolerance. The TREX1–condensate experiments described in the previous chapter show that DNA degradation depends on the environment in which the DNA resides, not only on the presence of an active nuclease. A condensate can preserve a ligand against a negative regulator and thereby change the time available for sensing. Such preservation remains a mechanism demonstrated in particular biochemical and cellular systems; it is not evidence that the same protected structures have been identified in human Alzheimer's brain.²⁸

More recent structural work by Zhu and colleagues identified determinants that enable TREX1 to recognize double-stranded DNA and restrain cGAS. A conserved arginine helped engage the non-substrate strand, and an additional human TREX1 DNA-binding surface contributed to restraint beyond nuclease catalysis alone. Experiments connected disrupted interfaces to increased pathway signalling and antitumor activity in mouse models. These findings refine the distinction between removing DNA chemically and competing for access to it.⁴⁰

The resulting interpretation is that effective disposal cannot be inferred solely from transcript abundance of a degradative enzyme. Activity also depends on substrate form, accessibility, and the

physical relationship between the enzyme and its target. A normal amount of TREX1 could therefore coexist, in principle, with poor clearance of a protected DNA population. That possibility is a testable inference about regulation, not a diagnosis of which disposal mechanism has failed in a given neurodegenerative model.

4.6 A framework for recognizing failure of self-tolerance

Taken together, these studies support several experimentally distinct forms of restraint: positioning of the sensor, inhibitory chromatin binding, competition for DNA, phosphorylation-dependent control, and disposal of available substrate. Their coexistence makes self-tolerance a maintained cellular function rather than the mere absence of injury. This formulation is useful because a disease-associated response may begin with a change in the sensor's access or restraint even when total cellular DNA is unchanged. It also permits a sustained response to emerge through continued substrate production without requiring an intrinsic defect in the enzyme.

For the Alzheimer's disease argument developed later, the central unresolved issue is which controls are altered in the relevant cells and whether their alteration precedes functional decline. A microglial response to mitochondrial DNA, a neuronal response to lysosomal stress, and a response to exposed chromatin should not be collapsed into the same initiating event. They may converge on cGAMP or STING while differing in how tolerance was breached. Their convergence is valuable for identifying shared intervention points, but their differences determine how a causal model should be tested.

The foundational literature therefore establishes the plausibility and experimental accessibility of persistent DNA-driven signalling without proving its prevalence in human disease. It supplies concrete mechanisms by which DNA can become visible, remain available, or activate a normally restrained enzyme. The subsequent disease chapters must add cell-specific, temporal, and intervention evidence before assigning those mechanisms to synaptic failure. That division of labor preserves the explanatory strength of cGAS–STING biology while preventing the pathway's breadth from becoming a substitute for disease-specific proof.

5. STING as a Moving Signalling Platform

5.1 Activation requires a place as well as a ligand

The name cGAS–STING can make two distinct proteins sound like a single switch. They instead occupy successive positions in a spatially organized system: cGAS produces a diffusible messenger, while STING converts messenger recognition into changes in membrane traffic and downstream activity. The distinction becomes especially useful when interpreting a persistent response. Excessive messenger production, prolonged residence of signalling-competent STING, and continued responsiveness to secreted interferon are different explanations for an inflammatory phenotype, even when the final transcriptional measurements look similar.

Mukai and colleagues established that relocation to the Golgi is mechanistically consequential, showing that palmitoylation of STING at membrane-proximal cysteines is required for efficient signalling in their experimental systems. Blocking the modification or changing the relevant residues suppressed downstream responses, including those produced by constitutively active disease-associated STING variants. The study therefore connected an organelle-specific protein modification to signalling competence, rather than treating movement away from the endoplasmic reticulum as an incidental imaging observation. It was a cell-biological demonstration, not evidence that Golgi palmitoylation is the rate-limiting lesion in Alzheimer’s disease.⁴¹

The downstream assembly is also more specific than a sequence of proteins drawn beside arrows. Liu and colleagues, in Chen’s laboratory, showed that phosphorylation of innate immune adaptors creates docking sites that recruit IRF3 for activation. STING and the RNA-signalling adaptor MAVS use related phosphorylation-dependent principles, despite receiving different upstream information. This explains how a shared kinase system can produce a coordinated interferon response while retaining distinct upstream routes. It also means that phosphorylated TBK1 alone does not identify the initiating sensor: adaptor engagement and genetic dependence are needed to establish the route.⁴²

NF- κ B requires separate attention. Balka and colleagues found that TBK1 and IKK ϵ can act redundantly in STING-induced NF- κ B responses in human and mouse immune-cell systems, whereas IRF3 activation was much more dependent on TBK1 kinase activity. A treatment that strongly reduces an IRF3 or interferon readout can consequently leave another inflammatory output relatively preserved. The practical inference is that an Alzheimer’s experiment should measure the branch it claims to modify, rather than use a single phosphorylation band as a surrogate for every STING function.⁴³

5.2 Autophagy and membrane physiology extend the pathway beyond interferon

Gui and colleagues demonstrated a TBK1- and interferon-independent autophagy function of STING. In their experiments, STING movement through the ER–Golgi intermediate compartment supported LC3 lipidation and the clearance of cytosolic DNA and viruses, with requirements that differed from conventional starvation-induced autophagy. A sea-anemone STING orthologue could induce autophagy without inducing interferon, supporting an evolutionary separation between these outputs. Chen’s contribution here is particularly relevant to a clearance-centred account of neurodegeneration: the DNA-surveillance apparatus can mobilize a disposal response as well as announce danger.⁴⁴

That finding does not make every increase in LC3 a sign of successful clearance. LC3 can accumulate because more membrane-associated processing has begun or because the resulting material cannot be removed. It can also be conjugated to single membranes, a process that should not be equated automatically with completion of a conventional double-membrane autophagosome pathway. For an experimental interpretation, flux matters: following material to degradation is more informative than counting puncta at a single time point. This is a methodological inference from the distinction between initiation and disposal, rather than a claim that all STING-associated LC3 structures have one identity.

Liu and colleagues subsequently provided evidence that human STING itself can conduct protons. Purified-protein experiments and cellular measurements connected its channel activity to organelle pH changes, LC3 lipidation, and inflammasome-related outputs; the small molecule C53 helped distinguish channel-associated effects from phosphorylation readouts. The importance of this result is conceptual as well as structural: membrane physiology is one of STING’s activities, not merely its operating environment. However, experimental deacidification of STING-bearing compartments does not establish that STING is the cause of the widespread lysosomal acidification defects reported in Alzheimer’s disease.⁴⁵

A further refinement appeared in 2026. Tan and colleagues identified PtdIns(3,5)P₂ as an endogenous lipid ligand that cooperates with cGAMP to support STING activation, and linked the response to PIKFYVE, the enzyme that generates this phosphoinositide. Their biochemical and cellular results place membrane lipid composition within the activation mechanism itself. The result should be stated as cooperation with cGAMP, not as evidence that this lipid generally replaces cGAMP. It also comes from molecular and cellular systems, so its consequences for Alzheimer’s neurons, glia, or therapeutic dosing remain to be determined.¹⁹

5.3 Degradation limits the duration of STING signalling

Kuchitsu and colleagues traced a termination route in which STING moves through recycling endosomes and is delivered for lysosomal degradation through ESCRT-dependent microautophagy. Their experiments connected ubiquitinated STING, recognition by the ESCRT component TSG101, and the physical incorporation of STING-containing vesicles into the degradative compartment. The result makes the off-switch tangible: signalling ends partly because the cell changes the location and ultimately the existence of the activated protein. Calling this merely “autophagy” loses the specific trafficking and membrane-remodeling steps that an experiment could test.⁴⁶

An independent study by Gentili and colleagues identified ESCRT-dependent control of both steady-state and cGAMP-induced STING degradation. Disrupting this machinery allowed STING to accumulate and sustain activity, while a disease-associated UBAP1 variant demonstrated that a pathological alteration in an ESCRT component could disturb the process. This provides evidence for control at baseline as well as after a strong experimental stimulus. It does not establish that every ESCRT disease phenotype is mediated by STING, nor that an Alzheimer’s-associated trafficking variant necessarily reproduces the same defect.⁴⁷

Balka and colleagues supplied convergent evidence in myeloid cells, linking defective ESCRT-dependent degradation to inadequate termination of STING responses. The value of agreement among these studies lies in the common functional result across different approaches: disposal machinery constrains the duration of signalling. Their detailed trafficking models need not be flattened into one universally obligatory sequence in every cell. For a brain-disease study, the reproducible question is whether disrupting the relevant disposal step changes the lifetime of active STING and the duration of its outputs in the particular cell population under examination.⁴⁸

Degradation is not the only means of reducing signalling competence. Li and colleagues showed that the phosphatase PPM1A dephosphorylates STING and TBK1 and disrupts their signalling assembly. This provides a distinct regulatory route and reinforces the need to measure protein abundance separately from phosphorylation and output. A reduced active-STING pool can reflect biochemical inactivation, physical disposal, or both.⁴⁹

5.4 The experiment must distinguish activation, persistence, and reception

A useful experimental design separates three clocks. The first follows the initiating material, such as cytosolic DNA or cGAMP; the second follows STING movement, modification, and disappearance; the third follows transcription and responses to secreted interferon. A persistent interferon-stimulated gene program after a brief trigger can arise because any one of these processes remains active. Conversely, a reduction in inflammatory RNA might reflect failed reception of interferon while the initiating cell continues to generate it. These alternatives are hypotheses to discriminate, not different names for the same mechanism.

The operational consequence is to use time-resolved perturbations wherever possible. A brief ligand pulse followed by washout asks whether the cell can terminate a completed challenge; continuous exposure asks about the balance between ongoing stimulation and suppression. Measuring total STING alongside its localisation and phosphorylation helps distinguish accumulation from activation. Combining cGAS loss, STING loss, and IFNAR interference then separates dependence on DNA sensing, the adaptor, and the downstream cytokine receptor, with appropriate controls for the other functions affected by each manipulation.

Table 1 — STING readouts and their interpretation

Observation	Interpretation that remains possible	Discriminating measurement
Persistent interferon-stimulated transcripts	Continuing production or prolonged cytokine reception	Paired producer-cell signalling and IFNAR-dependent response measurements
Increased total STING	More synthesis, failed disposal, or both	Turnover after a defined stimulus and direct trafficking analysis
More LC3-positive structures	Increased initiation or impaired completion	Cargo-specific flux and lysosomal delivery
Reduced phospho-IRF3	Suppression of one output branch	Independent NF- κ B, membrane, and functional readouts

These distinctions position termination as a tractable explanation for persistence without making it the default explanation. A strong result would show that a disease-relevant perturbation prolongs STING activity after the initiating signal has subsided, and that restoring disposal shortens that activity while preserving the ability to respond to a subsequent challenge. That would demonstrate a failure of resolution. If DNA and cGAMP instead remain elevated throughout the experiment, continued activation is still a viable explanation and may be the more important therapeutic target.

6. Sources of Self-DNA and the Boundaries of DNA Surveillance

6.1 DNA becomes inflammatory through access, not ancestry alone

The question is not simply whether a cell contains damaged DNA. It is whether DNA becomes accessible in a form and location that can activate the relevant sensor, and whether it persists long enough to exceed local restraints. Nuclear DNA, mitochondrial DNA, and reverse-transcribed mobile-element DNA offer different routes to this state. They should be treated as competing or cooperating candidate inputs, each with its own transport, packaging, and clearance requirements. An increase in total DNA damage does not by itself identify which input is responsible.

Structural work by Pathare and colleagues showed how nucleosome binding can restrain cGAS, providing a molecular explanation for why proximity to genomic DNA need not trigger continuous signalling. Binding at the nucleosome interface prevented the productive arrangement required for activation in their structural and biochemical systems. Thus, nuclear localisation cannot be interpreted as synonymous with enzymatic activity. For a disease study, the pertinent variables include DNA exposure and packaging as well as sensor abundance; localisation images should be paired with evidence of cGAMP production or downstream pathway dependence.⁵⁰ The article's August 2026 correction replaced a duplicated representative control image; the authors stated that the conclusions were unaffected.⁵¹

West and colleagues established that mitochondrial DNA stress can prime antiviral immunity through cGAS–STING. Perturbation of TFAM-dependent mitochondrial genome organization produced access to immunostimulatory mtDNA and elevated antiviral responses, linking mitochondrial genome maintenance to innate signalling. Their work is especially useful because it identifies a genome-packaging defect, rather than using reduced ATP as a stand-in for every consequence of mitochondrial injury. It supports mtDNA stress as one possible bridge from organelle dysfunction to inflammation, while leaving open whether that particular bridge dominates in an Alzheimer's cell or brain region.⁵²

Kim and colleagues identified another route: oxidatively stressed mitochondria released short mtDNA fragments through pores associated with VDAC oligomers, with consequences in lupus-related experimental systems. This is direct support for a membrane-escape mechanism, but the disease context and the fragment class are part of the finding. It should not be expanded into a claim that all mitochondrial genomes leave through VDAC or that every instance of impaired

respiration activates cGAS. The Alzheimer's hypothesis becomes stronger when DNA origin, fragment characteristics, and route of release are measured in the same model as the inflammatory phenotype.⁵³

6.2 Mitophagy is relevant, but its benefits do not establish a STING mechanism

Fang and colleagues reported impaired mitophagy in Alzheimer's-related material and showed that interventions promoting mitophagy improved pathological and functional outcomes in experimental models. Their work supports mitochondrial quality control as a disease-relevant process and provides reasons to study interactions between neurons and microglia. It does not, by itself, show that the reported benefits require cGAS–STING suppression. Improved organelle disposal can affect energy supply, oxidative injury, protein handling, and immune behaviour through several routes, so assigning all of the rescue to one sensor would exceed what that evidence demonstrates.⁵⁴

One formerly prominent shortcut in this literature must now be removed. The 2018 paper “Parkin and PINK1 mitigate STING-induced inflammation” was retracted in July 2025 after problems were identified with the reliability and reproducibility of specified data. Its reported animal rescues cannot be used here as established evidence for a PINK1/Parkin-to-STING causal chain. The retraction does not refute every relationship between mitochondrial quality control and inflammation; it removes a particular evidentiary support and requires that each remaining relationship be grounded in independent work.⁵⁵

For the present framework, mitophagy is therefore a candidate regulator of DNA supply rather than an assumed universal STING brake. A useful test would follow mitochondrial cargo into the degradative system, quantify cytosolic mtDNA with controls against fractionation contamination, and measure cGAMP before assigning causality. Rescue should then be tested for dependence on cGAS or STING. If an intervention improves neuronal physiology without changing those measurements, its benefit remains valuable, but it supports a different account of how mitochondrial maintenance preserves function.

6.3 Nuclear damage, mobile elements, and senescence provide distinct routes

Dou and colleagues showed that cytoplasmic chromatin fragments can activate cGAS–STING and contribute to inflammatory secretory programs in senescence and cancer models. This supplies an experimentally supported route from altered nuclear integrity to inflammation. It also illustrates why the context of a secretory response matters: signalling that promotes removal of damaged or premalignant cells can have a different consequence from prolonged exposure in a tissue with limited replacement capacity. Extension to ageing neurons requires evidence in those cells, rather than an assumption that every senescence-like marker implies the same chromatin-export process.⁵⁶

Mackenzie and colleagues identified ruptured micronuclei as another source of immunostimulatory chromatin, linking chromosome-segregation errors and genome instability to cGAS activity. Their demonstration is important precisely because much of the mechanism depends on cell division. It is consequently more immediately applicable to dividing glia and progenitors than to mature postmitotic neurons. Neuronal nuclear damage may still generate accessible DNA through other routes, but the micronucleus mechanism cannot be transferred wholesale without showing the relevant structures, history, and signalling in the neuronal setting.⁵⁷

De Cecco and colleagues showed that LINE-1 derepression can contribute to a late-senescence interferon response through reverse-transcription-dependent events. Their experiments connected endogenous mobile-element activity to inflammatory maintenance and showed that pharmacological interference with reverse transcription could reduce associated responses in their systems. This makes LINE-1-derived DNA a plausible self-generated input to a persistent alarm. It does not establish LINE-1 as the initiating cause of Alzheimer's disease or justify reading every retrotransposon transcript as proof of a cGAS-activating DNA intermediate.⁵⁸

These mechanisms can interact without becoming interchangeable. A damaged mitochondrion can contribute to nuclear stress; impaired degradation can prolong the life of DNA released from either compartment; and a changing chromatin state can alter mobile-element transcription. Those are candidate interactions to test, not a license to draw one compulsory progression from mitochondrial failure through LINE-1 to STING and senescence. A discriminating study should measure the proposed intermediate and establish its necessity. Otherwise, a shared interferon signature can make different causes appear deceptively identical.

6.4 RNA sensors and inflammasomes cannot be substituted for cGAS

Chen's work on MAVS provides a useful boundary. Seth and colleagues identified a mitochondrial adaptor required for antiviral signalling downstream of RIG-I, connecting an RNA-sensing route to IRF3 and NF- κ B. The fact that the adaptor resides on mitochondria does not make mitochondrial DNA its defining input. Nor does convergence on interferon establish that an upstream cGAS mechanism was engaged. In an endogenous viral-mimicry model, RNA and reverse-transcribed DNA should be distinguished experimentally because they can recruit different sensors while producing overlapping transcriptional outputs.⁸

DNA itself can also engage different immune machinery. Hornung and colleagues established that AIM2 recognizes cytosolic double-stranded DNA and assembles an ASC-dependent, caspase-1-activating inflammasome. This is a different output architecture from cGAS production of cGAMP and STING-mediated transcriptional signalling. Consequently, a DNA-associated inflammatory phenotype is not enough to choose between these pathways. Readouts of messenger production and receptor-adaptor dependence answer different questions from measurements of inflammasome assembly and cytokine maturation.⁵⁹

NLRP3 adds another boundary. Shimada and colleagues connected oxidized mitochondrial DNA to NLRP3 inflammasome activation in primed macrophage experiments, supplying one mechanism by which mitochondrial injury can support inflammatory cytokine processing. That result concerns a particular activation context and should not be interpreted as a universal direct DNA-sensor description of NLRP3. Neither IL-1 β release nor an interferon signature establishes the whole proposed chain by itself. Interactions between STING and inflammasome activity need their own temporal and genetic tests.⁶⁰

Table 2 — DNA sources and sensor boundaries

Candidate input or event	Principal route considered here	What the observation does not establish
Accessible mitochondrial or nuclear dsDNA	cGAS → cGAMP → STING	That the DNA is the dominant source of inflammation
Endogenous or viral RNA	RNA sensors → MAVS or other adaptors	That reverse-transcribed DNA or cGAS is required
Cytosolic dsDNA with ASC/caspase-1 assembly	AIM2 inflammasome	That STING-mediated interferon caused the response
Primed-cell mitochondrial stress with cytokine maturation	NLRP3-associated activation	A compulsory linear cGAS → NLRP3 cascade

The useful synthesis is therefore a branching map of surveillance systems. Cell damage can feed several routes, and the products of one route can alter the responsiveness of another. A claim of convergence becomes informative when it specifies the shared measurement or dependency, rather than treating every marker of inflammation as one process. This distinction is particularly important for a synaptic-resilience argument: preventing a neuronal interferon response, reducing myeloid cytokine maturation, and improving organelle disposal may all preserve function while operating at different causal positions.

7. Disease Evidence: Ageing, Tau and Amyloid

7.1 The causal claim must match the model

Evidence that cGAS–STING participates in neurodegeneration comes from interventions with different starting conditions. Normal ageing asks whether the pathway contributes to deterioration without introducing an Alzheimer transgene. Tauopathy asks whether it changes the consequences of a defined tau insult, while amyloidosis models ask how it modifies a system driven by amyloid production and deposition. These questions are complementary, but a positive answer to one does not establish the temporal order of the others in sporadic human disease.

Three distinctions organize this evidence. A pathway can alter the amount of pathology, the injury caused by a given amount of pathology, or the capacity to recover after injury. A lower plaque or tau measurement supports the first possibility; preserved function at comparable pathology supports the second; recovery requires measurements before and after intervention. Keeping these outcomes separate prevents the word “rescue” from concealing different biological achievements.

The distinction also changes what counts as an adequate control. When an intervention lowers the initiating burden, an accompanying reduction in inflammation may be secondary to that change. When burden remains stable, downstream protection becomes more plausible, although an unchanged bulk measurement cannot exclude a shift in the species or location that matters. Establishing mediation therefore requires a measured intermediate and a perturbation that selectively changes its contribution.

7.2 Normal ageing supplies an independent entry point

Gulen and colleagues connected mitochondrial disturbance and cytosolic mitochondrial DNA in aged microglia to cGAS–STING activity. STING inhibition reduced inflammation and improved functional measures in aged mice, while a microglial cGAS gain-of-function model supplied evidence that activating the pathway could itself produce adverse brain outcomes. The study also examined senescent human cells and tissues; those experiments were not a treatment study in people with dementia. Its distinctive contribution is a route into inflammatory deterioration that does not require an amyloid or tau transgene.⁶¹

An earlier study by Baruch and colleagues located an ageing-associated type I interferon signature at the choroid plexus in mice and human tissue. Interferon-receptor blockade in aged mice improved aspects of cognition and neurogenesis. This work established an anatomically different interferon-associated mechanism, without identifying cGAS as its necessary upstream sensor. The choroid plexus observation is therefore evidence for the breadth of interferon biology in ageing, not permission to assign every age-associated interferon signal to microglial DNA sensing.⁶²

Together, these studies suggest a spatial question rather than a single origin. A brain may contain an initiating compartment, a cytokine-producing population and several responding populations whose locations do not coincide. Sampling only the strongest transcriptional responder could misidentify the source. The relevant map must distinguish production, reception and injury, and should allow signals at a brain interface to coexist with locally generated parenchymal signals.

7.3 Tau can engage the pathway without becoming its canonical ligand

Udeochu and colleagues found that pathogenic tau elicited microglial cGAS–interferon responses, partly associated with mitochondrial DNA escape. In P301S tauopathy mice, Cgas deletion preserved synaptic and cognitive outcomes without lowering the measured pathogenic tau burden; pharmacological inhibition also supported functional protection. The downstream neuronal MEF2C network provided a candidate resilience mechanism. This is evidence that injury can be modified beyond the amount of tau detected, within the tested mouse model. It does not establish that tau directly occupies the DNA-binding surface of cGAS.⁶³

Jin and colleagues supplied another route from extracellular tau to innate signalling. They identified an interaction between tau and PQBP1 and used inducible microglial Pqbp1 depletion, together with cGAS/STING perturbations, to connect tau sensing to inflammatory outputs. Their experiments emphasized PQBP1-dependent recognition and NF- κ B-associated responses. This result concerns a protein-recognition component upstream of the pathway; it should not be rewritten as proof that a protein aggregate replaces DNA in the canonical cGAS catalytic reaction.⁶⁴

The relationship between these routes remains experimentally useful rather than logically settled. PQBP1 could affect an early recognition or uptake event, whereas mitochondrial injury could supply a later activating nucleic acid; alternatively, their importance could differ with tau preparation and cellular state. These are hypotheses about dependencies, not conclusions obtained by drawing a single arrow through both studies. Comparing tau species, internalization, DNA escape and cGAMP production in the same preparation would establish whether the routes are sequential, convergent or condition-specific.

7.4 Amyloid studies include changes in pathological burden

Xie and colleagues reported evidence of microglial cGAS–STING activation in human Alzheimer tissue and examined causality in 5×FAD mice. Cgas deficiency improved cognitive and inflammatory outcomes together with amyloid-associated pathology, and STING inhibition with H-151 produced additional intervention evidence. Experiments involving microglia and astrocytes implicated a glial relay in protection from oligomeric Aβ toxicity. The mouse intervention is causal evidence within the model, while the human tissue evidence locates an associated pathway state rather than demonstrating clinical treatment efficacy.⁶⁵

Chung and colleagues extended the intervention literature to AppNL-G-F/hTau double-knock-in mice. STING inhibition affected amyloid burden, tau phosphorylation, microglial synapse engulfment and memory-related outcomes. Their cellular work connected Aβ and tau exposure to mitochondrial stress and ectopic DNA, and also examined APOE-related effects. The study complicates a simple expectation that STING blockade must erase every interferon-associated microglial transcript: some transcriptional responses differed from the overall direction of tissue inflammation.⁶⁶

The comparison matters because functional improvement accompanied by less pathology does not identify the same causal route as improvement without a change in measured pathology. Both can justify further investigation, but they nominate different mediators and trial endpoints. It would be premature to choose between an exclusively upstream “clearance” explanation and an exclusively downstream “resilience” explanation across these models. A pathway can influence both, with their relative contributions changing as the initiating insult and cellular environment change.

Table 3 — Disease models and the conclusions they support

Experimental setting	Principal question	Interpretation that remains unjustified
Natural ageing	Does pathway manipulation modify age-associated decline?	Every effect is specific to Alzheimer disease.
Defined tauopathy	Can injury be uncoupled from measured tau burden?	Every toxic tau species remained unchanged.
Amyloidosis or combined pathology	Does intervention alter the burden–inflammation–injury system?	Functional benefit must arise entirely downstream of deposits.
Postmortem human tissue	Is the proposed state present in relevant cells?	A cross-sectional association establishes onset, mediation or reversibility.

7.5 Human cellular evidence is necessary but not equivalent to an aged human brain

Suptela and colleagues examined genotoxic injury in a human microglial cell line. Radiation and oxidative stress produced inflammatory responses that were reduced by cGAS-directed genetic perturbations and STING inhibition, supporting a self-DNA-sensing mechanism in human-derived cells. The preparation was an immortalized microglial line, which is a consequential qualification when interpreting DNA damage, proliferation and innate response thresholds. It establishes experimental competence of a pathway, not the prevalence or intensity of that pathway in an aged cortical microglial population.⁶⁷

Human-derived cells, postmortem specimens and mouse interventions solve different parts of the translation problem. Human cells permit controlled perturbation but may lack ageing history and tissue interactions. Postmortem tissue preserves disease context but supplies an endpoint after variable agonal and handling conditions. Animal experiments connect molecular changes to physiology and behaviour, but their exposure history and genetic construction constrain generalization. Agreement across these sources is strongest when each measures the same molecular operation rather than merely a similarly named expression signature.

A particularly important distinction is between expression and activation. More cGAS, STING or an interferon-stimulated transcript can motivate a mechanism, but it does not independently identify the activating DNA, demonstrate cGAMP synthesis or establish the duration of signalling. Human mapping should therefore seek combinations of cell identity, pathway state and tissue context. A single bright marker cannot carry all three inferences.

7.6 Emerging findings broaden the upstream search

A 2026 study by Hao and colleagues linked Tet2 deficiency to oxidative stress, mitochondrial DNA escape and cGAS–STING-associated responses. It combined observations in amyloid-positive human variant carriers with constitutive mutant mice and microglial perturbations; antioxidant treatment improved several experimental outcomes. This identifies an additional candidate connection between epigenetic maintenance and DNA sensing. Because an antioxidant changes processes beyond cGAS, improvement with that intervention does not by itself establish that pathway inhibition uniquely mediates the benefit.⁶⁸

Gene names alone cannot resolve the direction of an effect. Bouzid and colleagues reported an association between clonal hematopoiesis and lower Alzheimer dementia risk, with additional analyses of blood-derived clones and brain myeloid cells. That observational finding concerns somatic hematopoietic clones, not constitutive Tet2 loss across a mouse or an isolated microglial knockdown. It should neither be ignored nor treated as a direct contradiction without accounting for cell lineage, mutation timing and selection.⁶⁹

The resulting constraint is constructive: every proposed upstream cause needs a specified genetic state, cellular compartment and time of action. “TET2 affects inflammation” is too broad to predict whether changing it in an adult brain will help. A meaningful connection to cGAS requires showing which DNA pool changes and whether selective interruption of its sensing changes injury. This standard also prevents a growing list of upstream stressors from becoming an explanation that can accommodate any result.

8. Downstream Consequences and the Responding Cell

8.1 Interferon is a mediator with several possible origins

Roy and colleagues identified interferon-associated responses near nucleic-acid-containing amyloid and tested type I interferon signalling in experimental synapse loss. Their interventions supported an IFN–complement relationship and a contribution of microglial responses to synaptic injury. The distinction from IFN- γ was explicit: the implicated type I response should not be replaced by a generic statement about “interferon.” Equally, a requirement for IFNAR establishes a responding pathway; it does not retrospectively identify cGAS as the necessary sensor in every condition that induced it.⁷⁰

This separation is central to causal interpretation. Blocking a receptor shared by several upstream stimuli can suppress an endpoint even when the nominated initiating sensor is dispensable. Conversely, inhibiting one sensor may leave enough cytokine production from other routes to sustain the response. The cGAS-specific question and the interferon-dependence question therefore require separate perturbations and should produce separate claims.

8.2 Microglial and neural IFNAR are not interchangeable targets

In a subsequent amyloid-model study, Roy and colleagues used a reporter and cell-directed *Ifnar1* deletions to distinguish responding populations. Microglial deletion reduced loss of postsynaptic terminals associated with selective engulfment, whereas neural deletion restored presynaptic terminals and reduced plaque accumulation. Broader IFNAR blockade improved memory and synaptic outcomes. These results give a concrete reason to retain the pre- and postsynaptic distinction and to avoid describing a neural-lineage manipulation as necessarily restricted to mature neurons.⁷¹

A field-level measurement of synaptic protein could combine those effects into a single apparent improvement. That would obscure whether the intervention preserved an axon terminal, prevented removal of a postsynaptic structure, altered plaque-associated exposure or affected several processes. The difference is not semantic: each mechanism predicts a different spatial relationship and a different response to delayed intervention. A useful downstream model must identify the cell that receives the cytokine as carefully as the cell that produces it.

8.3 Two MEF2C stories occupy different cells

Deczkowska and colleagues showed that chronic type I interferon exposure and ageing were associated with reduced microglial Mef2C and altered inflammatory responsiveness. Their work positions microglial Mef2C as a restraint on inflammatory reactivity. It does not establish that a measurement of total hippocampal MEF2C reports the same process, because that signal includes neuronal and other cellular contributions. A decrease in a transcription factor acquires mechanistic meaning only after its cell type and regulated outputs are specified.⁷²

Barker and colleagues identified MEF2-associated transcriptional programs through environmental enrichment in mice and human cognition-linked transcriptomic analyses. Experimental manipulation supported a role for MEF2 in cognitive potential and protection against neurodegenerative challenge. The human association and mouse intervention are mutually informative but remain distinct evidence classes. A human cognition-correlated gene network is a candidate explanation of resilience, not a direct measurement of its causal contribution in an individual patient.⁷³

The tau-cGAS study discussed above places an interferon-dependent change in the neuronal MEF2C network downstream of microglial activation. That neuronal mechanism should be distinguished from the microglial Mef2C response described in ageing.⁶³ A model can include both without requiring identical regulation, identical timing or identical effects of restoring the factor. The discriminating measurements are cell-specific transcriptional activity and function, rather than a pooled abundance value.

8.4 Complement can connect inflammatory state to physical removal

Hong and colleagues demonstrated complement- and microglia-associated synapse loss before overt plaque deposition in experimental Alzheimer models. Perturbing components of the complement pathway protected against defined synaptic effects. This supplies an independent reason not to assign all complement-related injury to a late response to established plaques. It does not, by itself, place cGAS upstream of that early event or establish that all complement-derived fragments act through one receptor.⁷⁴

Complement changes need to be described at the level of the fragment and responding cell. Increased C3 expression, deposition of a cleavage product, receptor engagement and engulfment

are different observations. An interferon-associated increase in one component does not automatically demonstrate more functional tagging of viable synapses. Connecting those observations requires measuring processing and localisation alongside the fate of the synapse, particularly when bulk tissue measurements combine astrocytic production, neuronal surfaces and microglial uptake.

8.5 TNF and astrocytes introduce another relay

Gulen and colleagues directly distinguished cytokine dependencies in their microglia–neuron co-culture experiments. TNF blockade rescued neuronal death, whereas type I interferon receptor blockade did not. The result locates a damaging output in that preparation and prevents the ageing phenotype from being reduced to a single IFN-I branch. It remains compatible with an IFN-dependent synaptic mechanism in a different tauopathy experiment.⁶¹

Liddel and colleagues showed that a combination of microglial IL-1 α , TNF and C1q induced a neurotoxic reactive astrocyte state in their experimental systems. The induced state persisted after removal and neutralization of the initiating cytokines in the tested culture conditions. This supplies a concrete example in which a downstream cellular response can outlast an initiating exposure. It neither identifies cGAS as the upstream cause nor means every reactive astrocyte in Alzheimer tissue belongs to one uniform toxic state.⁷⁵

The implication for a persistent-alarm model is that persistence may move between levels. Continued neuronal dysfunction after a fall in interferon could reflect a maintained astrocytic program, unresolved physical damage or another ongoing stimulus. It would not immediately prove that STING itself remains active. Conversely, stopping one cytokine while leaving cooperating signals intact could make a reversible process appear autonomous. Time courses must therefore separate the initiating pathway from downstream state and function.

Table 4 — Cell-specific downstream responses

Candidate downstream effect	What establishes the proposed level	Common inference to avoid
Microglial synapse engulfment	Cell-specific signalling perturbation plus synapse-fate measurements	More internal fluorescent material necessarily means more uptake.
Neuronal transcriptional vulnerability	Neuronal target engagement and functional dependence	Whole-tissue MEF2C abundance identifies the responding cell.
Persistent astrocytic response	Removal of the initiating exposure with continued state and functional measurements	Persistent injury proves persistent cGAS or STING activity.

8.6 MHC-I offers a plausible bridge with important boundaries

The neuronal MHC-I literature establishes physiological functions independently of cGAS. Corriveau and colleagues connected neuronal activity to class I MHC expression, and Huh and colleagues demonstrated roles in circuit refinement and synaptic plasticity.^{76, 77} Syken and colleagues identified neuronal PirB as an MHC-I-associated restraint on cortical plasticity; Lee and colleagues subsequently demonstrated that neuronal H2-Db expression could restore developmental synapse elimination in a relevant MHC-I-deficient background. These results support specific neuronal functions, not a universal rule that increasing MHC-I causes pathological pruning.^{78, 79}

The interferon-to-MHC-I bridge is also preparation-dependent. Massa and colleagues found efficient neuronal antiviral responses to IFN- β despite deficient induction of MHC-I genes, whereas Funk and Lotz described a primary embryonic hippocampal-neuron assay in which IFN- β induced measurable surface MHC-I.^{80, 81} Thus, an interferon response cannot substitute for measuring the proposed neuronal ligand. Maturation, neuronal population and culture conditions are potential determinants to test rather than explanations to assume.

Brott and colleagues established C4d as a ligand for LirB2/PirB in their assays and demonstrated PirB-dependent spine loss after cortical C4d exposure.⁸² That distinct route makes receptor occupancy and ligand identity essential variables in any integration. A cGAS-IFN-MHC-I-PirB chain remains a testable hypothesis until interventions place those nodes in order in the relevant tissue. Receptor abundance, complement staining and interferon signatures cannot collectively establish the missing dependency by association alone.

9. Resilience, Human Genetics and APOE

Christchurch

9.1 Protection can change exposure or susceptibility

The word resilience is most informative when the challenge is specified. Preserving cognition despite high amyloid burden can involve less tau accumulation, greater tolerance of tau, better circuit compensation or a combination of those processes. Consequently, “resilient to amyloid” and “resilient to tau” need not describe the same individual or experiment. Molecular studies should state the pathology against which function is preserved and the features of that pathology actually measured.

This distinction is especially useful for a pathway that might affect both inflammatory amplification and clearance. A protective variant could reduce the delivery of a harmful cargo before innate sensing begins. It could instead reduce the response to comparable cargo, or improve disposal after sensing has occurred. These possibilities can yield similar endpoint pathology while predicting different responses to a drug introduced after disease is established.

9.2 The human observation preceded the proposed cGAS mechanism

Arboleda-Velasquez and colleagues described a PSEN1-E280A carrier homozygous for APOE3 Christchurch whose cognitive impairment was markedly delayed despite substantial amyloid burden. The case also showed unusually limited tau-associated pathology relative to the amyloid finding and motivated investigation of altered ApoE interactions. It was an exceptional human natural experiment, but a single individual could not isolate one protective biochemical pathway from all other inherited and acquired influences. The report did not directly demonstrate cGAS suppression as the mediator of protection.⁸³

Quiroz and colleagues subsequently studied heterozygous Christchurch carriers within the same autosomal-dominant Alzheimer population. Twenty-seven carriers were compared with a much larger noncarrier population, with a median onset of cognitive impairment approximately five years later in the carrier group; the delay was smaller than in the homozygous case. This strengthened the genotype–phenotype association beyond one person while retaining constraints imposed by sample size, shared ancestry and the PSEN1 mutation context. It did not establish that pharmacological inhibition of one downstream pathway would reproduce the genotype's lifetime effects.⁸⁴

The temporal difference is important. A germline variant operates before the first pathological event and can alter cell development, decades of exposure and compensatory responses. An inhibitor administered after symptoms begins from a different biological state. Human genetic protection can therefore nominate mechanisms and establish plausibility without specifying the reversibility, timing or magnitude of a therapeutic effect.

9.3 Experimental cGAS evidence supplies a mechanistic candidate

Naguib and colleagues replaced mouse Apoe with human APOE3 or its homozygous R136S form on a tauopathy background. Christchurch reduced tau burden and protected synaptic, myelin and network measures; mouse and human-derived microglial experiments showed diminished tau-evoked cGAS–STING–interferon responses. A cGAS inhibitor preserved synapses and produced transcriptional changes overlapping those associated with the variant. This triangulates a mechanistic contribution, but pharmacological resemblance does not establish that every protective effect is mediated by cGAS, or that this mediation explains the human carriers' delayed disease.⁸⁵

A stronger exclusivity claim would require reversing the proposed mediator while retaining the protective genotype and demonstrating loss of the relevant protection. Even then, the result would apply to the challenged preparation and measured outcome. The practical aim need not be exclusivity: identifying a reproducible, drug-accessible component could be valuable while other protective mechanisms remain active. The appropriate claim is the component established, rather than the entire phenotype assigned to a single node.

9.4 Related Christchurch models do not all produce one phenotype

Nelson and colleagues examined the R136S substitution on an APOE4 background in mouse tauopathy and human-derived neuronal models. Homozygosity protected several pathological outcomes, whereas heterozygosity partially protected neurodegenerative and inflammatory measures without the same tau-pathology effect. This shows that allele dosage and APOE background can separate outcomes often grouped under protection. It does not justify assuming that an APOE3 result has identical quantitative consequences on APOE4.⁸⁶

Y. Chen and colleagues used humanized APOE3 Christchurch mice and human Alzheimer tau inoculation to study amyloid-associated tau seeding and spread. They connected the variant to altered plaque-associated microglial responses and increased myeloid uptake and degradation of tau aggregates, alongside altered proteoglycan interactions. This provides a clearance-related mechanism that deserves to remain visible beside cGAS–interferon suppression. A mechanism that changes the amount or presentation of tau could also change the stimulus reaching an innate sensor.⁸⁷

Tran and colleagues introduced the Christchurch substitution into mouse Apoe and compared amyloid and tau models. The variant enhanced a disease-associated microglial response around plaques but dampened glial responses to tau; in the tau model, selected synaptic and myelin measures improved without reduced tau accumulation or phosphorylation. The direction of a microglial signature therefore depended on the challenge. A transcriptional label such as “disease-associated” cannot by itself determine whether the response is helpful or harmful.⁸⁸

These results motivate comparisons at matched biological states rather than only matched chronological ages. Animals of the same age can differ in burden, cellular exposure and prior injury, and a protective genotype can itself cause those differences. Automatically adjusting for pathology could remove part of the genuine genetic effect, while failing to measure it could obscure the mechanism. Analyses should distinguish the total protective effect from the narrower response to comparable exposure.

9.5 Human cells and lipid trafficking identify additional mechanisms

Sun and colleagues used a human iPSC-based system to show that Christchurch microglia could protect neurons against A β -associated tau pathology. Their work implicated altered lipid peroxidation and phagocytic behaviour. The controlled cellular design supports a microglial contribution in that system, while leaving open which aspects depend on cGAS signalling. It also illustrates why uptake, oxidative stress and neuronal injury should be measured together rather than inferred from a common inflammatory marker.⁸⁹

Guo and colleagues studied lipidated ApoE–receptor interactions and lysosomal consequences. Christchurch variants and ApoE2 showed reduced receptor-dependent uptake, while ApoE and its lipid cargo could generate adverse lysosomal outcomes under the tested conditions. Their work supplies a cargo-delivery mechanism distinct from simply lowering a cytokine response. Connecting that mechanism to DNA escape would require direct evidence that altered cargo handling changes the relevant nucleic-acid exposure, rather than assuming that any lysosomal improvement must silence cGAS.⁹⁰

Perez-Corredor and colleagues reported altered Christchurch interactions with tau and Dickkopf-1, with biochemical and experimental evidence relevant to tau aggregation and pathology. These observations add extracellular or direct protein-interaction possibilities to the mechanistic set. They do not refute a role for microglial innate signalling; they prevent its premature elevation to the sole explanation. A protective allele can modify several interacting surfaces, and different preparations may expose different consequences of that change.⁹¹

9.6 Genetic support and mediator support are different claims

The human Christchurch findings support a relationship between a defined APOE variant and delayed disease in a particular familial context. The experimental studies nominate mechanisms through which the variant can alter pathology or injury. Joining the two is a scientific inference that becomes stronger as the same intermediate is demonstrated across human carriers, human cellular preparations and perturbable models. Neither a strong genetic association nor an elegant mouse mechanism can supply the missing measurement in the other evidence class.

Table 5 — Genetic protection and evidence of mediation

Claim	Evidence needed	Present interpretive boundary
A variant protects people	Replicated genotype–phenotype association with appropriate population analysis	Protection can be context- and allele-dose-dependent.
cGAS contributes to a model phenotype	Selective manipulation with pathway and functional measurements	Contribution is established for the tested model and endpoint.
cGAS mediates variant protection	Manipulation of the mediator within the protective genotype	Phenocopy alone cannot establish complete mediation.
A drug reproduces human resilience	Human target engagement, tolerability and meaningful clinical benefit	Genetic and preclinical observations do not substitute for a clinical test.

9.7 What resilience contributes to the larger model

The strongest contribution of resilience biology is the requirement to measure preserved function alongside pathology. It encourages testing whether a cell can encounter an insult, contain its consequences and resume useful activity. It also makes persistent inflammatory signalling an experimentally tractable candidate: the question becomes whether the response remains proportionate to the challenge and whether changing its duration preserves function. The duration itself, however, must be measured rather than inferred from a single inflammatory endpoint.

For cGAS–STING, the resulting position is specific. The disease-model evidence warrants investigation of DNA sensing as a contributor to synaptic vulnerability, and the Christchurch studies provide an independent route for selecting mechanistic comparisons. Neither evidence stream establishes one universal cause of Alzheimer disease or one necessary explanation of human resilience. Their productive intersection is a set of cell- and state-specific dependencies that can be tested without requiring every protective effect to pass through the same pathway.

10. Lysosomal Termination: Disease Mechanisms and Limits

10.1 A disposal defect can prolong the alarm

The most direct connection between the present pathway and a clearance-centred Alzheimer's framework is the demonstration that lysosomal degradation can limit the lifetime of activated STING. The ESCRT studies establish that trafficking and degradation constrain its signalling lifetime, making disposal capacity a possible determinant of inflammatory duration. This yields a specific hypothesis: a cell with impaired terminal processing may remain inflammatory after an otherwise manageable insult. The hypothesis is narrower and more testable than the general proposition that lysosomal dysfunction causes neuroinflammation.^{46, 47}

A second possibility is that lysosomal dysfunction increases the supply of accessible DNA, so that the alarm is repeatedly reactivated rather than merely left on. These explanations can coexist, but their therapeutic implications differ. Accelerating STING disposal would address prolonged adaptor residence; reducing DNA exposure would address continuing sensor stimulation. The distinction also prevents a common interpretive error: a STING-dependent rescue does not, on its own, reveal whether the original lesion lay in DNA generation, messenger signalling, trafficking, or degradation.

10.2 NPC1 studies show why cGAS dependence must be measured

Chu and colleagues identified NPC1 as a factor in STING trafficking to lysosomes and described two linked effects of NPC1 loss: increased permissiveness for STING trafficking through association with SREBP2-related transport, and impaired terminal degradation. In their *Npc1*-deficient mouse experiments, deletion of *Sting1* or *Irf3* improved neurological and inflammatory phenotypes, whereas deletion of *Cgas* did not provide the corresponding rescue. The result supports a cGAS-independent STING mechanism in that setting. It therefore directly challenges any rule that STING activation in a lysosomal disorder must be explained by excess cytosolic DNA acting through cGAS.⁹²

Wang and colleagues later studied several lysosomal-storage disorders and found neuron-intrinsic cGAS–STING activation associated with accumulation of cytoplasmic double-stranded DNA. Their work included genetic, nuclease-based, and lysosome-directed interventions, with benefits in models of Sandhoff, Fabry, and Niemann–Pick disease. In *Npc1*-deficient animals, neuronal TREX1 delivery improved selected neurological and

neuronal-survival outcomes. These observations support DNA-dependent disease mechanisms in their experimental program, but should not be rewritten as though they simply confirm the cGAS-independent explanation in the earlier NPC1 study.⁹³

The responsible synthesis preserves the disagreement at the level where it exists. Differences in cell populations, background, disease stage, perturbation, and endpoint are possible explanations, but none should be declared the resolution without a direct comparison. Neuron-targeted DNA digestion is also not experimentally identical to whole-animal loss of cGAS. For Alzheimer's research, the lesson is to measure dependencies within the proposed model: determine whether reducing DNA, removing cGAS, and removing STING produce the same rescue, partial rescues, or different phenotypes. Divergence among those results is information about mechanism.

10.3 C9orf72 supplies another precedent, not an Alzheimer's equivalence

McCauley and colleagues showed that C9orf72 deficiency in myeloid cells can impair STING degradation and enhance STING-associated inflammatory signalling. Their study linked mouse genetics to interferon-related signatures in material from people with C9orf72 repeat-associated ALS/FTD, creating a bridge between trafficking biology and a human neurodegenerative context. This makes C9orf72 a useful precedent for the proposition that defective disposal can amplify innate immunity. It does not mean that C9orf72-associated disease, sporadic Alzheimer's disease, and a generic lysosomal stress assay share the same initiating lesion or dominant cell type.⁹⁴

Cross-disease evidence should be used to define experiments rather than erase disease boundaries. In this case, it suggests following STING degradation and cytokine persistence after manipulating an Alzheimer's-relevant trafficking factor, then testing whether restoration of that factor normalizes both. A change in total lysosomal abundance would be inadequate: enlarged or more numerous compartments can coexist with poor processing. The essential result would be restored handling of the relevant cargo together with an appropriate change in signalling duration and the neuronal or glial function that motivated the experiment.

10.4 The Alzheimer's bridge remains a hypothesis requiring direct linkage

Lee and colleagues documented early autolysosomal acidification abnormalities and intraneuronal accumulation of amyloid-related material in several Alzheimer's mouse models, with related morphology in human disease tissue. This gives the clearance framework a defined neuronal defect and an observable disease-associated phenotype. It does not show that impaired STING degradation produced the phenotype, that cGAS was activated in the affected neurons, or that STING inhibition would restore autolysosomal function. The proposed connection to the persistent alarm should therefore be presented as a synthesis across separate experiments, not a result already demonstrated within that study.⁹⁵

The decisive experiment would connect both halves in the same preparation. It would establish the acidification or trafficking defect, measure STING delivery and decay after a controlled challenge, and show whether restoring lysosomal function changes the response. Parallel measurements of cytosolic DNA and cGAMP would distinguish failed termination from renewed activation. A neuronal or synaptic endpoint is then necessary to show why the altered alarm matters, rather than merely adding an inflammatory marker to a familiar lysosomal phenotype.

10.5 STING can also participate in lysosomal recovery

Tang and colleagues provide an important counterweight to a purely destructive interpretation. They found a STING–TFEB pathway that supported lysosomal gene expression and recovery from damage through STING’s proton-channel function, independently of its interferon-signalling branch. Their work included lysosomal-storage-disease models and cellular recovery assays, indicating that STING can recruit compensatory machinery as well as inflammatory outputs. The implication is not that prolonged STING activity is beneficial in Alzheimer’s disease, but that complete pathway suppression may remove useful functions alongside harmful ones.⁹⁶

The lipid connection also operates at termination. Shoji and colleagues identified a lysosomal PI(3,5)P2–CHMP4B mechanism required for microautophagic degradation of STING, linking a membrane phosphoinositide to the ESCRT machinery that completes disposal. Read together with the activation work described in Chapter 5, this shows why the effect of altering a lipid-producing enzyme cannot be predicted from one arrow in a pathway diagram. A perturbation may affect both entry into signalling and eventual removal, depending on compartment and timing. Neither study establishes the net effect of that perturbation in Alzheimer’s disease.⁹⁷

The resulting research objective is selective restoration of a bounded response: enough surveillance to detect and handle damage, followed by effective resolution before persistent signalling undermines tissue function. That objective is an inference from the combination of activation, disposal, and recovery evidence; it is not yet a validated treatment strategy. It calls for measurements of host-response competence and lysosomal recovery alongside inflammatory suppression. In a synaptic-resilience framework, the most persuasive intervention would preserve neuronal function while showing exactly which pathological response it shortened and which useful functions remained intact.

II. Convergence on the Synapse: Receptor Restraint and Inflammatory Context

11.1 A shared endpoint does not establish a shared route

The cGAS–STING literature and the neuronal receptor literature both reach synaptic outcomes, but they begin in different compartments and often measure different processes. A dendritic spine can shrink because neuronal signalling changes, disappear after a microglial interaction, or become functionally ineffective while its structure remains visible. The integration problem is to identify which route contributes to a particular outcome under a particular exposure. Synapse counts alone cannot assign that route.

The work of Carla Shatz and colleagues provides a defined receptor entry point. Kim and colleagues reported A β oligomer binding to human LILRB2 and mouse PirB and linked the mouse receptor to synaptic plasticity deficits in an Alzheimer model. These findings establish a neuronal receptor mechanism within the tested systems. They do not identify cGAS as an upstream requirement or make the biochemical functions of LILRB2 and PirB identical in every experimental context.⁹⁸

Brott and colleagues subsequently identified C4d as a LILRB2/PirB ligand and showed that cortical C4d infusion reduced spine density in wild-type mice, with protection in the PirB-knockout comparison. Human array tomography supplied a complementary anatomical view of receptor and ligand-associated material at synapses. This combination offers a tractable route for asking whether a defined receptor response interacts with an inflammatory state. It does not by itself demonstrate how endogenous cGAS activation would generate that state or the relevant ligand exposure.⁸²

11.2 The MHC-I connection as a mediation problem

The proposed bridge from IFN-I through neuronal MHC-I to PirB-mediated restraint has several separately testable steps. First, the exposure must produce the relevant neuronal surface molecules. Second, those molecules must engage the receptor in a configuration that alters signalling. Third, the resulting receptor activity must contribute to a defined synaptic outcome. Demonstrating the first step and observing the last does not establish the middle one.

A useful experiment would hold the initiating inflammatory exposure constant while altering neuronal IFNAR, the relevant MHC-I presentation machinery, and PirB separately. If neuronal IFNAR loss prevents both the surface change and the synaptic response, the result places neuronal

interferon reception upstream of those outcomes. PirB perturbation and re-expression should be restricted to neurons, with baseline synaptic and plasticity controls because receptor manipulation can itself alter restraint. If neuronal PirB loss preserves synapses while the interferon response remains intact, the receptor becomes a candidate mediator. If the synaptic deficit survives PirB loss, a parallel effector remains necessary to explain it.

The negative outcomes are informative. A failure to induce surface MHC-I in one preparation would identify a limitation of that model or exposure rather than disprove all interferon effects. A preserved IFN-induced synaptic deficit in a PirB-null preparation would bound the proposed receptor bridge without contradicting IFN-dependent microglial uptake or neuronal transcriptional change. Interpretation should follow the specific intervention and endpoint rather than the broad disease label.

It is also necessary to distinguish the ligand classes. A β , C4d and MHC-I are not interchangeable measures of receptor occupancy. Their physical presentation, affinity, availability and competing interactions differ. A study that changes the amount of one ligand cannot assume that another ligand contributes in the same direction. The pathway described in Chapter 8 becomes a receptor-mediated hypothesis only when those molecular details are specified.

11.3 Receptor abundance, ligand availability and occupancy

High receptor immunoreactivity is compatible with several different functional states. It may represent more receptor at the surface, accumulation in an intracellular compartment, altered epitope accessibility or an increased fragment pool. Even when the surface pool is known, receptor abundance does not establish what fraction is occupied. A correlation between receptor intensity and injury therefore cannot identify the ligand or prove that receptor engagement caused the injury.

Hofer and colleagues' work illustrates the importance of presentation. They observed uptake of soluble C4d associated with ILT4/LILRB2 in immune-cell systems, while binding of soluble receptor to the tested complement-deposited C4d was not detected. These observations make the physical form of the ligand an empirical variable. They do not establish the duration of neuronal receptor signalling or show that uptake necessarily terminates it.⁹⁹

For a tissue study, receptor abundance, accessible ligand and a downstream activity readout should be recorded as separate quantities. Local plaque distance can be a spatial covariate, but it is not a direct measurement of occupancy. The distribution of IFN-responsive glia can be another covariate, but it is not a cGAS assay. A richer map becomes useful when its variables preserve their biological meanings rather than being collapsed into a single label of exposure.

11.4 EphB2–Ephexin5 as a distinct candidate coupling

The proposed EphB2–Ephexin5 relationship supplies another synaptic mechanism that may interact with inflammatory context. Cissé and colleagues linked A β exposure to proteasomal depletion of EphB2 and demonstrated functional rescue by restoring EphB2 in an experimental Alzheimer model. Margolis and colleagues established EphB-dependent regulation of Ephexin5 phosphorylation, ubiquitination and degradation during synapse development. These findings motivate a test of whether receptor loss and substrate persistence occur at the same diseased synapses.^{100 101}

The contemporary interpretation must also accommodate Ephexin5's physiological contribution to Cdc42 signalling and activity-driven spine growth, demonstrated by Petshow and colleagues. An increase in total Ephexin5 cannot therefore be classified as an increase in one uniformly harmful activity. Its location, phosphorylation, partners and context all matter. The appropriate claim is a possible change in coupling between receptor signalling and substrate fate.¹⁰²

Adding cGAS to this account changes the set of competing explanations. An inflammatory exposure could alter synthesis of one protein, trafficking of another, the survival of particular synapses, or the composition of the sampled neuronal population. Any of these could change a cross-synapse correlation. The correlation remains a useful observation, but a turnover mechanism requires dynamic measurements and an intervention that changes the proposed coupling.

The most informative integration would ask whether blocking the inflammatory route changes receptor–substrate coupling while leaving the initial ligand exposure measurable. Conversely, restoration of receptor function could be tested while the inflammatory state persists. A rescue that depends on both operations would support an interaction; two independently protective interventions would leave open parallel pathways. These are different conclusions with different therapeutic implications.

11.5 Trafficking as an interaction point

Han and colleagues reported that persistent PirB cleavage generates a C-terminal fragment associated with Golgi-directed trafficking deficits and impaired cathepsin-D maturation. Much of the mechanistic work concerned mouse PirB, alongside a limited human comparison of LILRB2 fragment abundance. The study creates a specific candidate connection between a neuronal restraint receptor and organelle dysfunction. It does not demonstrate that the fragment causes STING activation or delays STING disposal.¹⁰³

An interaction with STING would require the relevant cargo and cell type to be identified. A neuronal Golgi defect might affect neuronal STING, alter the production of material later sensed by microglia, or change synaptic receptor traffic without engaging DNA sensing. These alternatives

predict different locations of cGAMP production and different responses to cell-specific knockouts. Merely placing both mechanisms in a drawing of the endolysosomal system cannot choose among them.

The experiment should therefore follow two fates in parallel: the receptor-derived fragment and activated STING. If altering fragment production changes STING residence without changing its initial activation, a termination interaction becomes plausible. If it changes DNA release and cGAMP before STING activation, the interaction lies upstream. If both molecular trajectories are unchanged while synapses improve, the rescue may operate through another cargo altogether.

Table 6 — Distinguishing the proposed synaptic routes

Route	Necessary discriminating observation	What an association alone leaves open
IFN-I → neuronal receptor restraint	Receptor-specific intervention changes the IFN-dependent synaptic effect	Parallel neuronal or microglial effectors
EphB2 → Ephexin5 persistence	Receptor manipulation changes endogenous substrate turnover	Altered synthesis, selection or redistribution
PirB fragment → STING persistence	Fragment manipulation changes STING clearance kinetics in a defined cell	A common trafficking stress acting on both
Inflammatory microglia → synapse removal	Cell-specific intervention changes uptake and functional synapse survival	Debris clearance after independently initiated injury

12. A Dynamic Model of Initiation, Residence and Recovery

12.1 Why a static pathway diagram is insufficient

A pathway diagram specifies possible relations but ordinarily leaves their time scales implicit. That omission is consequential when the proposed lesion is persistence. A short burst of DNA release can generate a longer inflammatory response through ordinary downstream delays. Repeated small inputs can resemble one continuous input. A durable transcriptional response can outlast both the initiating DNA and the activated signalling complex.

The following model is a proposed analytical framework, not a fit to biological data. Its purpose is to identify quantities that must be measured to distinguish continued activation from defective

termination. It intentionally omits many known feedbacks. A more elaborate model would be useful only when the data could constrain the additional parameters.

Let D denote the accessible DNA pool within a defined sensing compartment, G the local cGAMP pool, S the activated signal-competent STING pool, F an extracellular inflammatory mediator, and E a downstream effector state in a specified recipient cell. Each variable refers to one experimentally defined quantity rather than to a global score of disease severity. The same notation can be applied separately to microglia and neurons, but their parameters should not be assumed equal.

Proposed minimal model

$$dD/dt = J_D(t) - k_D D$$

$$dG/dt = v_{cGAS}(D, C) + J_{import} - (k_{hydrolysis} + k_{export}) G$$

$$dS/dt = a(G, L, C) (S_{total} - S) - k_{term} S$$

$$dF/dt = q S - k_F F$$

$$dE/dt = b F - k_E E$$

Here J_D is the rate at which DNA becomes accessible, k_D its removal rate, L the relevant membrane-lipid context and C other local regulatory conditions. The cGAMP equation separates local enzymatic production, import, hydrolysis and export. These fluxes cannot be inferred from messenger abundance alone. The activation function a need not be linear. The parameter k_{term} combines loss of signalling competence and removal of activated STING; these processes can be split when the experiment measures them separately. Treating S_{total} as constant is a short-window approximation that requires verification. Degradation changes the total pool unless synthesis compensates, and a longer experiment should model inactive and active protein pools separately. The final two equations describe production and decay of a mediator and a recipient-cell state.

12.2 Five routes to an apparently persistent alarm

In the first route, J_D remains elevated. The cell continues to supply DNA to an otherwise normally regulated sensor. Reducing cGAS activity may lower downstream output while the upstream damage persists. When inhibition ends, the response can resume because the substrate source remains present. This is continued initiation rather than evidence of an intrinsically defective STING off switch.

In the second route, k_D falls. DNA accumulates because its removal is slow, even if the rate at which new material appears has not increased. Measuring a large cytosolic DNA pool cannot distinguish this case from increased production. A pulse-labelled substrate or a source-selective

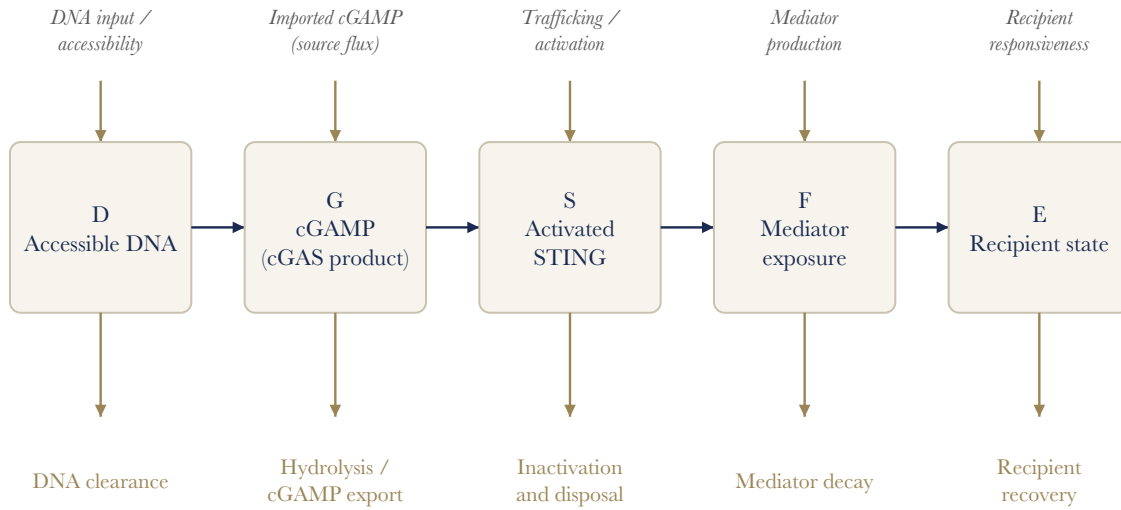
intervention is needed to separate the two. Restoring removal and suppressing sensing can produce similar short-term inflammatory changes but different long-term trajectories.

In the third route, the cGAMP pool persists because hydrolysis or export falls, or import from another cell continues. A recipient cell can consequently remain exposed to messenger even when its own DNA-sensing activity is low. Measuring local cGAS abundance or removing only the recipient's enzyme would not resolve that possibility. The relevant comparison tracks cGAMP in the source, extracellular space and recipient alongside transporter or hydrolase perturbations qualified for that preparation.

In the fourth route, k_{term} falls. Activated STING remains competent to signal for longer. In this case, cGAMP generation may normalize before STING activity does. Replenishment of the activated pool through altered trafficking is a separate possibility that belongs in an activation or recycling input, rather than automatically implying slower termination. A downstream antagonist could reduce output without demonstrating that the residence defect has been repaired. The relevant observation is the fate of the activated pool after a controlled input.

In the fifth route, k_E is small. The recipient cell retains a downstream state after the upstream mediator declines. A persistent transcriptional programme, altered protein inventory or structural injury could create this pattern. The equations do not assert which biological process supplies the memory. They show why recovery of cGAMP or interferon to baseline does not by itself establish recovery of synaptic function.

A causal schematic: no fitted parameters and no measured trajectories



cGAMP synthesis and import are separate from STING residence and mediator decay.

Figure 3. Author-proposed analytical framework, not measured data: $D \rightarrow G \rightarrow S \rightarrow F \rightarrow E$. cGAMP (G) is a distinct state with local synthesis, import, hydrolysis, and export. Separate inputs and removal rates govern each state; prolonged output alone does not identify the defect.

12.3 What a washout experiment can establish

A washout experiment is informative only when the removed variable is identified. Removing extracellular tau does not prove that internalized tau or newly exposed DNA has disappeared. Removing an inhibitor does not prove that its intracellular effect has ended. Replacing culture medium does not necessarily remove a matrix-associated mediator. The practical definition of time zero must therefore be supported by a measurement of the relevant input.

An ordered series would measure accessible DNA and cGAMP near initiation, STING localisation and activity through the intermediate interval, and mediator release and recipient-cell responses over a longer interval. The timing should be established empirically rather than borrowed from a different cell type. Sampling density must be sufficient to observe the rise as well as the decline. A single late point cannot distinguish a delayed peak from slow termination.

The most useful comparison combines a defined pulse with interventions at different positions in the pathway. If cGAMP falls below its effective activation range while a matched activated-STING pool remains signal competent, the result supports persistence downstream of ongoing messenger supply. Continued local or imported cGAMP must be excluded. If mediator output declines before the recipient response resolves, that response relaxes more slowly; this alone does not establish a self-maintaining state. Slow protein turnover, structural injury and other inputs remain possible explanations. These comparisons test ordering without presupposing that every component follows a single exponential decay.

12.4 Identifiability and the danger of fitting too much

At steady state in the simplest DNA equation, D equals J_D divided by k_D . Measuring D alone cannot identify both terms. The same ambiguity recurs at subsequent stages: a high mediator concentration can reflect greater production, slower removal or both. An impressive fit to a static measurement does not resolve that ambiguity. Parameters require interventions or time-resolved observations that affect them differently.

A related problem arises when the measured material is a mixture of cells. More activated microglia can increase a tissue-level signal even if the signal per microglial cell is unchanged. A reduction in the number of viable neurons can increase a ratio without increasing the numerator within surviving cells. Models should therefore preserve absolute counts, cell identities and distributions wherever possible. A normalized ratio is a useful derived quantity whose denominator remains part of the explanation.

The aim is not to produce a maximal mathematical description. A minimal model that distinguishes two experimentally plausible mechanisms is more useful than a large network whose parameters cannot be estimated. The proposed model earns its place only if it changes sampling, intervention order or interpretation. It should be revised when the data reveal a missing compartment or a response that violates its assumptions.

12.5 Recovery as an independent experimental endpoint

Suppressing an inflammatory marker establishes a biochemical effect. Recovery requires an additional observation about the tissue function that mattered before treatment. For a synaptic experiment, relevant quantities include survival of previously functional contacts, restoration of evoked responses and renewed capacity for plasticity. The choice depends on whether the intervention is intended to prevent loss, reverse dysfunction or support replacement.

These objectives should be separated in time. A treatment given before an insult tests prevention. A treatment given after the molecular response is established tests whether the process remains modifiable. A treatment followed by a drug-free interval tests whether the improvement

persists. None is a substitute for the others, and an experiment can succeed at one while failing at another.

The dynamic framework consequently changes the meaning of a therapeutic target. A molecule may initiate injury without remaining necessary to sustain it. Another may be dispensable at initiation but necessary for a persistent downstream state. A third may participate in both damage and recovery in different compartments. The useful target is defined by causal position, timing and tissue outcome together.

13. An Experimental Programme from DNA Sensing to Functional Synapses

13.1 The programme begins with a discriminating question

The central experimental question is whether a specified synaptic deficit requires cGAS-dependent initiation, STING-dependent persistence, a downstream inflammatory response, or an interaction with neuronal receptor signalling. Answering it requires a sequence of experiments rather than a large panel of loosely related markers. Each stage should establish a dependency needed by the next. An unsuccessful stage should narrow the interpretation instead of being bypassed by adding another correlation.

The proposed programme has four linked components: qualification of measurements; identification of the initiating and responding cells; dynamic tests of signalling persistence; and confirmation of anatomical relevance in human tissue. Its endpoints are molecular and functional. It is not a clinical protocol, and the interventions described are research manipulations rather than treatment recommendations. Sample sizes and exposure conditions must be determined from the chosen preparation and observed variance.

An appropriate initial preparation is one in which both the input and the recipient-cell response can be controlled. A defined neuron–microglia culture permits cell-specific manipulations and conditioned-medium transfers. An organotypic slice preserves more local architecture but complicates attribution. Human cellular systems provide species relevance, while their maturation and donor history remain variables to measure rather than assumptions to inherit.

13.2 Qualification of the molecular measurements

The initial measurement panel should distinguish cGAS presence from activity. Total protein or transcript abundance shows that a sensing capacity may exist; it does not show that the enzyme produced its messenger. cGAMP measurement provides a more proximal activity readout, provided the assay identifies the relevant nucleotide and its recovery from the sampled compartment. Compartmental cGAMP abundance reflects synthesis, hydrolysis and transport; attribution to local cGAS production requires source-specific perturbation or flux evidence. Measurements of activated STING and downstream kinase or transcription-factor states then test whether messenger availability propagated into signalling.

Antibody qualification must be specific to the application. A reagent that detects a band in a lysate may not recognize the same protein after fixation and resin embedding. Micheva and colleagues developed a screening strategy that models the relevant processing conditions for array tomography. Their work supports a qualification stage before a new antigen is used to assign molecular states at individual synapses. Genetic negative controls and an independent assay are particularly valuable when a spatial correlation is the intended endpoint.¹⁰⁴

For DNA measurements, the qualification problem is contamination as much as detection. A cytosolic fraction can acquire nuclear or mitochondrial material during processing. Imaging can place a DNA signal near an organelle without resolving whether it lies inside or outside its membrane. An informative workflow uses independent localisation and fraction-purity controls and reports the fraction of samples that fail them. A large numerical signal with uncertain compartment assignment cannot establish cytosolic sensing.

The same principle applies to degradation. Loss of a fluorescent signal can reflect photobleaching, epitope change, export or destruction. A pulse-labelled protein, an orthogonal abundance assay and a compartment marker can help separate these possibilities. Inhibiting a degradative process can be informative, but the intervention may also alter activation and transport. The inference should follow the joint measurements rather than the name of the inhibitor.

13.3 Locating the initiating and responding cells

A mixed culture should be treated as an experimental system with several possible causal arrangements. cGAS can be manipulated in the putative source or sensor cell while STING and IFNAR are manipulated in the putative recipient. The design should include conditions in which only one cell population is altered. A whole-culture knockout can establish a pathway contribution but cannot locate the relevant step.

Conditioned-medium experiments test whether a transferable factor is sufficient under the collection and exposure conditions. They do not establish its identity. A recipient response that survives IFNAR blockade may involve another cytokine, a nucleotide messenger, extracellular

vesicles or contaminating material. A response that disappears after transfer could require contact, rapid local signalling or a labile factor. These alternatives should remain explicit until a selective intervention distinguishes them.

The proposed comparison uses matched donor cells, cell-type-specific cGAS and STING perturbations, and recipient IFNAR perturbation. It measures the initial DNA/cGAMP response, a defined mediator panel, neuronal transcriptional changes and synaptic function. Re-expression of the perturbed component provides an additional control when feasible. The objective is to assign the causal step to a cell, not merely to produce a protective manipulation.

Table 7 — An ordered set of pathway-bypass tests

Intervention and challenge	Question	Interpretation requiring confirmation
cGAS loss, followed by cGAMP delivery	Is the defect upstream of STING reception?	Rescue requires adequate delivery and functional STING
STING loss, followed by supplied IFN-I	Can the recipient response occur downstream of STING?	Rescue establishes downstream competence, not the endogenous mediator's identity
Neuronal IFNAR loss during glial stimulation	Does neuronal interferon reception contribute?	Separate neuronal effects from changes in glial feedback
PirB loss during defined IFN-I exposure	Is the proposed restraint receptor necessary?	A residual deficit supports additional effector routes
DNA-source intervention after signal initiation	Does continuing DNA exposure sustain the response?	Measure cGAMP and STING decay separately

13.4 Testing termination after a controlled input

The termination experiment should begin with a reproducible input that produces a measurable response without overwhelming the cells. After the input is withdrawn, accessible DNA, cGAMP, STING localisation, STING activity and mediator release should be followed on their own time scales. The initial magnitude should be matched across conditions when the question concerns decay. Otherwise a larger initial response can masquerade as a longer-lived one simply because it takes longer to cross the detection threshold.

The critical comparison is between an intervention that reduces new activation and one that changes the fate of an already activated pool. Introducing the intervention only after the response is established helps distinguish those effects. If a perturbation reduces the initial peak and the subsequent tail together, it may act at initiation. If the initial response is preserved but the tail changes, a role in persistence becomes more plausible.

Experiments on the STING disposal machinery require additional functional measurements because the same organelle system handles many cargos. A change in lysosomal pH, degradative enzyme maturation or membrane repair can alter both signalling and cell viability. An apparent anti-inflammatory effect accompanied by failed digestion or increased neuronal stress would be a different result from restoration of normal resolution. The outcome should therefore include the competence of the surrounding compartment.

The model-specific differences discussed in Chapter 10 make this stage essential. A cGAS inhibitor and a STING inhibitor should not be treated as interchangeable tools. If one is protective and the other is not, the first questions concern target engagement, timing, species sensitivity and the presence of alternative STING functions. Only after those are addressed should the difference be assigned to pathway independence.

13.5 Measuring synaptic survival and function

The primary synaptic outcome should be chosen before unblinding and should identify what is being preserved. Spine density is a structural measure; it is not identical to the number of functioning excitatory connections. Presynaptic and postsynaptic markers help identify appositions, while electrophysiological or activity-dependent measurements assess function. Longitudinal imaging adds the ability to distinguish loss of existing contacts from altered formation of new ones.

Microglial uptake requires particular care. More synaptic material inside a microglial cell can mean increased removal of living synapses, increased clearance of debris, or slower digestion after uptake. A single endpoint image cannot distinguish these. Pairing a pulse of labelled material with measurements of the source synapses and subsequent cargo degradation makes the interpretation more specific. A protective intervention should ideally preserve functional contacts rather than merely reduce the intracellular visibility of synaptic debris.

Array tomography supplies a complementary endpoint in fixed tissue. Micheva and Smith established the method's capacity to combine serial ultrathin sections with repeated antigen labelling and ultrastructural information. It can ask whether the molecular states implicated by dynamic experiments occur in particular synapses and their surrounding cellular environment. The method remains an anatomical measurement; it does not convert a fixed sample into a record of molecular turnover.¹⁰⁵

For the EphB2–Ephexin5 question, the analysis should include absolute signals, the chosen size normalization and an alternative treatment of synaptic size. A common denominator can introduce correlation into two otherwise independent measurements. Selection of only surviving, segmentable synapses can also change the observed distribution. These issues are reasons to examine the robustness of the association, not reasons to assume that any particular direction of correlation is artefact-free.

13.6 Human tissue and the inference it can support

Human tissue is most informative after a dynamic experiment identifies a precise molecular prediction. The prediction might concern activated STING in a defined glial population, a neuronal IFN-responsive state, or the spatial relation between those states and altered synaptic proteins. Tissue can establish whether that combination occurs in the sampled human disease stage. It generally cannot establish whether the combination initiated the disease or persisted for a specified duration.

A useful cohort includes pathology, cognitive status, region, age, sex, post-mortem interval and tissue handling as distinct variables. Individuals with substantial pathology and relatively preserved cognition are especially informative for resilience, but they are not automatically a biologically uniform group. Differences in regional pathology, co-pathology, reserve and survival can all influence the comparison. The analysis should preserve those possibilities rather than assign resilience to one marker in advance.

Donor-derived cell systems can help connect human variation to perturbation experiments. They also introduce a specific age limitation: Mertens and colleagues found that directly converted neurons retained ageing-associated signatures that were lost through pluripotent reprogramming in their comparison. This does not make one model universally superior. It means that a study of age-dependent DNA compartment failure should establish which features of age its cellular preparation retains.¹⁰⁶

13.7 Experimental units, masking and interpretable negative results

The independent experimental unit is ordinarily the animal, donor or independently prepared culture, not each cell or synapse imaged within it. Thousands of synapses can improve estimation within one donor without creating thousands of independent biological replicates. A hierarchical analysis can use the nested observations while keeping uncertainty tied to the level at which the intervention or diagnosis varies. Sample-size planning should be based on variation at that level.

Masking should extend through image acquisition, segmentation and endpoint extraction. Exclusion rules, including antibody failure and poor fraction purity, should be specified before diagnosis or intervention groups are revealed. A qualification failure is a result about the measurement, whereas a biological null is a result obtained with an adequate measurement. Combining them would conceal the difference between an uninformative experiment and evidence against the proposed mechanism.

The most useful negative result is one that excludes a meaningful effect within a preparation known to be competent to respond. Positive controls must therefore establish that the receptor, enzyme or recipient pathway was present and manipulable. A proximity-screen miss is weak evidence against a transient or intercellular connection if detectability was never established. A null

from a direct mediation experiment can be much stronger because its alternative explanations have been narrowed deliberately.

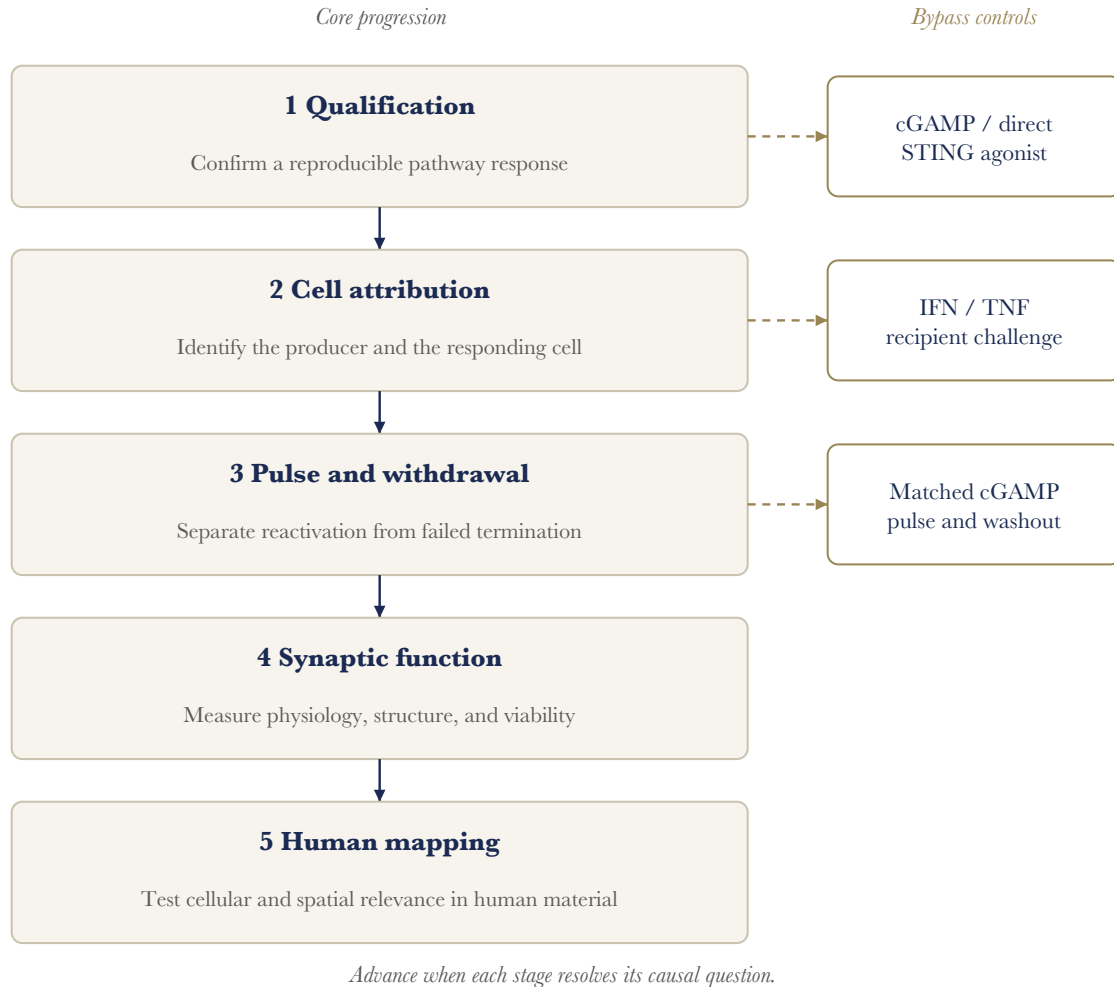


Figure 4. Author-proposed analytical framework. Each stage answers a different causal question. Bypass challenges test whether a defect lies upstream of STING, in signaling resolution, or in the recipient response. Human mapping assesses relevance after mechanism is defined.

14. Therapeutic Translation: Target, Compartment and Timing

14.1 The target is a causal position

The appeal of cGAS inhibition is that it acts close to one source of inappropriate inflammatory signalling. Its limitation follows from the same position: it will not necessarily block an independently activated STING pool or reverse a downstream state that no longer requires new cGAMP. STING inhibition acts further downstream but may affect a broader set of functions. IFNAR intervention addresses one response branch while leaving other inflammatory or membrane-associated functions available. The appropriate choice depends on which process remains necessary at the intended treatment stage.

This reasoning should not be converted into a universal ranking of drug targets. A more proximal intervention can be selective for the initiating lesion yet ineffective after propagation. A downstream intervention can suppress a damaging effector yet leave upstream injury unresolved. A compartment-repair strategy can reduce the source of the signal while also changing protective pathways. Comparative experiments must measure both the desired outcome and the biological operation each intervention changes.

14.2 Chemical probes and species dependence

Vincent and colleagues developed the cGAS inhibitor RU.521 and established activity in cellular experiments involving the mouse enzyme and autoimmune-model macrophages. Lama and colleagues subsequently developed inhibitors optimized for human cGAS and demonstrated why potency against the mouse enzyme cannot simply be transferred to human cGAS. These studies make species-matched target engagement an essential condition for interpreting a negative or positive pharmacological experiment. A shared pathway diagram does not imply a shared dose-response curve.^{107, 108}

Haag and colleagues identified covalent STING antagonists, including H-151, and connected inhibition to activation-associated palmitoylation. These compounds are valuable mechanistic probes, but their use does not make every downstream effect uniquely attributable to the intended node. Chemical specificity, exposure, cell viability and an independent genetic comparison remain important. The relevant inference is strongest when pharmacology and genetics agree on a defined molecular dependency.¹⁰⁹

For a brain indication, target engagement must be established in the relevant CNS compartment. Plasma exposure does not establish free concentration in brain tissue, and a whole-brain measurement can obscure differences among cells and regions. Peripheral immune modulation can also influence CNS outcomes without requiring direct inhibition in neurons or microglia. A successful animal experiment should therefore report the relationship between systemic exposure, CNS exposure and local pathway response.

14.3 Clinical development and the boundary of current evidence

The clinical development of cGAS inhibitors demonstrates that the target has progressed beyond laboratory probes. Ventus reports that VENT-03 completed a phase 1 programme and entered a phase 2 study in lupus; the AERIS trial is registered as NCT07260877. These are autoimmune-disease development activities. They do not establish efficacy in Alzheimer's disease, exposure in the ageing human brain, or the safety of long-duration CNS pathway suppression.^{110 111}

The distinction matters because the criteria for a useful Alzheimer intervention extend beyond short-term suppression of a blood interferon signature. The relevant population may have decades of pathology, multiple coexisting lesions and varying degrees of irreversible circuit loss. A biomarker-positive subgroup could be more informative than an undifferentiated diagnostic population, but the biomarker would need to predict dependence on the targeted mechanism. Expression of cGAS alone would be inadequate for that purpose.

A translational sequence would establish peripheral and central pharmacology, demonstrate a mechanism-specific biomarker response, and then evaluate a functional endpoint appropriate to disease stage. It should also test whether biomarker changes precede, accompany or fail to predict functional benefit. A marker that changes reliably with drug exposure can be useful pharmacodynamically without being a surrogate for cognition. Those roles should remain separate during development.

14.4 Preserve the functions required for recovery

Innate immune signalling participates in host defence and in tissue responses to damage. The preceding chapters also describe STING-associated functions that can support lysosomal adaptation and repair. Consequently, a decrease in inflammatory output is insufficient to establish that a treatment improves the tissue's overall ability to maintain itself. The therapeutic objective is a beneficial balance of damage control, response and recovery in the relevant cells.

This balance may differ among compartments. Reducing a prolonged microglial inflammatory response could be beneficial while reducing a neuronal repair function could be harmful. Altering the same pathway in peripheral immune cells could change susceptibility to infection or the handling of circulating inflammatory signals. These are mechanistic tradeoffs to measure in

development, not grounds for assuming that intervention is either uniformly dangerous or uniformly protective.

Timing offers another possible source of selectivity. A treatment might be given during a period when a persistent inflammatory state remains reversible, or intermittently if that restores resolution while retaining useful responses. These are hypotheses about therapeutic scheduling, not established clinical strategies. Their value depends on whether the relevant biological state can be measured and whether a drug-free interval preserves the desired improvement.

14.5 Combination hypotheses require interaction tests

Combining an inhibitor of inflammatory initiation with a therapy that restores neuronal receptor competence is mechanistically plausible. It is not justified merely because both interventions improve a similar endpoint when used separately. A factorial design can determine whether the effects are additive, redundant, antagonistic or dependent on treatment order. That distinction matters before a broad combination is described as a repair programme.

For example, an inflammatory intervention might preserve synapses only when neuronal signalling can recover. Conversely, restoration of a neuronal receptor might fail while inflammatory removal continues. A third possibility is that either intervention alone is sufficient because both affect the same limiting step. The experiment must retain molecular readouts for both arms if it is to distinguish those explanations.

The same caution applies to lysosomal interventions. A drug that changes acidity, transport or biogenesis acts on many substrates and may alter STING activation as well as disposal. A beneficial effect on one cargo is not evidence of generalized restoration. The more precise claim is that a specified operation improved under a specified condition, with a measured consequence for signalling and synaptic function.

Table 8 — Translation questions that remain open

Decision	Evidence needed before the decision is justified
Inhibit cGAS rather than STING	Continuing dependence on cGAS-derived cGAMP supply, an identified source compartment, and comparative target engagement, functional benefit and effects on useful STING outputs
Target IFN-I reception	A damaging IFNAR-dependent branch with acceptable effects on other responses
Repair trafficking or lysosomes	Cargo-specific recovery accompanied by resolution of the relevant signal
Select patients by a pathway biomarker	Evidence that the biomarker predicts mechanism dependence and clinical response
Combine immune and synaptic interventions	An interaction test with molecular and functional outcomes for both arms

15. A Mechanistic Account of the Persistent Alarm

15.1 What the evidence supports

The cGAS–STING system supplies a defined biochemical route by which misplaced DNA can alter a cell and its neighbours. Chen’s discoveries made the sensor, messenger and receiver experimentally separable. The subsequent structural and cellular literature explains why their activity depends on molecular presentation and compartmental context. The ageing and neurodegeneration literature establishes that parts of this system can contribute causally to synaptic and neuronal dysfunction in specific experimental models.

The evidence also establishes that the outputs are heterogeneous. A neuronal transcriptional programme, a microglial uptake response and TNF-dependent toxicity are not interchangeable observations. Nor are DNA-dependent initiation, delayed STING disposal and STING-associated lysosomal repair. An integrated account must explain why an intervention changes one outcome in one preparation without promising the same effect across every cell and disease state.

Human findings make the programme relevant but do not complete its causal chain. Genetic resilience, human tissue associations and clinical development in autoimmune disease each answer a different question. Their combination motivates targeted experiments and translational work. It

does not substitute for evidence that a specified intervention preserves cognition in people with Alzheimer's disease.

15.2 What remains a hypothesis

The proposed integration is that some forms of synaptic injury persist because damage-derived inputs, signal residence and recipient-cell states fail to resolve on compatible time scales. cGAS–STING can participate at several positions in that process. A neuron–microglia circuit could continue to amplify injury after its original trigger has diminished, but the existence and dominant direction of that circuit must be established in each model. The review supplies a way to test it without assuming the answer.

The connection to MHC-I–PirB/LILRB2 signalling remains particularly valuable because it can be tested as a mediation problem. A defined inflammatory exposure, neuronal receptor perturbation and functional synaptic endpoint can distinguish a receptor-dependent branch from parallel effects. The EphB2–Ephexin5 and receptor-fragment hypotheses can be examined with the same discipline. Their integration requires demonstrated changes in molecular fate, not simply shared association with Alzheimer pathology.

15.3 The next decisive result

The next decisive result would identify a persistent signal in a defined cell, show why it persists, and demonstrate that correcting that particular persistence restores a meaningful synaptic function. Such a result would connect molecular mechanism to tissue outcome through intervention and time. It could be positive or negative for cGAS as the best target, depending on where the remaining dependency lies. Either outcome would make the therapeutic question more precise.

The enduring contribution of the Chen programme is the experimental standard embodied in that question: separate the components, identify what each does, and reconnect them with measurements that establish order. Applied to the ageing brain, that standard turns the persistent alarm from a broad metaphor into a set of molecular trajectories that can be challenged, measured and, where the evidence permits, changed.

16. Experimental Definitions and Interpretation Guide

16.1 A glossary tied to measurements

The following definitions are operational. They specify what a measurement must establish before the corresponding term is used in the interpretation. They are intended to prevent common substitutions between abundance, activation, persistence and injury.

Table 9 — Operational definitions for a mechanistic experiment

Term	Operational meaning in this paper
Accessible DNA	DNA shown to be available to a specified sensor in a defined compartment
cGAS activity	Messenger production attributable to cGAS, distinguished from protein abundance
STING activation	Acquisition of a defined signalling or functional state, with its readout specified
STING residence	The duration of a labelled or otherwise traceable STING pool in a defined location/state
Type I interferon response	A measured IFNAR-dependent response, distinguished from a nonspecific inflammatory signature
Synaptic resilience	Retained or recovered synaptic function under a stated pathological challenge
Synapse removal	Loss of a defined contact, distinguished from redistribution of a marker
Clearance	Removal or destruction of specified cargo from a specified compartment
Termination	Decline of a defined signal after its relevant input is controlled
Recovery	Restoration of a stated function, measured separately from marker suppression

16.2 A compact decision sequence

When a tissue shows elevated inflammatory markers, the first question is whether the relevant cells have been identified. If the signal comes from a changing mixture of cells, within-cell activation remains unresolved. The next question is whether proximal pathway activity has been measured. A transcript signature can motivate the hypothesis but cannot identify cGAS as its sole source.

When cGAMP is elevated, the source and fate of its generating DNA become important. Increased DNA availability can arise from production, impaired removal or altered compartment access. A measurement of the pool should therefore be paired with an intervention that distinguishes at least two of these possibilities. Without that comparison, a claim about a particular organelle failure remains provisional.

When activated STING persists, the initiating input must be followed over the same interval. Continued ligand supply and slow disposal can coexist, and a downstream marker can outlast both. The experiment should measure the decline of each relevant component rather than choose one as a proxy for the entire pathway. A fitted half-life is interpretable only for the molecular pool actually tracked.

When synapses improve after intervention, the result should be classified as prevention, rescue of dysfunction, preservation of existing contacts or support of replacement. These outcomes can have different biological requirements. The classification also determines which follow-up matters: a durability test, a mechanism test, an exposure study or an anatomical confirmation. Calling all improvements “neuroprotection” loses useful information.

16.3 Claims that require an additional experiment

Table 10 — Observations that require further experiments

Observation	Premature conclusion	Additional experiment
More cGAS protein	More cGAS catalytic activity	Messenger assay with cGAS dependence
More STING in lysosomes	Successful signal termination	Time-resolved activity and degradation
Lower interferon signature	All STING output suppressed	Branch-specific functional measurements
More synaptic cargo in microglia	More killing of functional synapses	Longitudinal source tracking and digestion measurements
High LILRB2 at damaged synapses	Ligand-driven receptor injury	Occupancy/activity measurement and receptor perturbation
Rescue after constitutive knockout	Adult therapeutic reversibility	Intervention after onset with target engagement
Benefit in an amyloid mouse	Benefit in sporadic human AD	Human mechanism evidence and appropriately designed clinical studies

16.4 A minimum record for a reproducible mechanistic claim

A mechanistic report should make clear which organism and cell types were studied, how their age and maturation were defined, and which variable was manipulated. It should identify the relevant reagent, its specificity evidence and the conditions under which it was used. The timing of exposure, withdrawal and measurement must be recoverable from the report. These details define the experiment's meaning rather than merely its reproducibility.

The analysis record should identify the independent experimental unit, the primary outcome, the treatment of nested observations and the handling of exclusions. It should show whether the conclusion depends on a particular normalization, threshold or subgroup. A negative result should include the measurement's ability to detect a biologically meaningful response. A positive result should include an alternative explanation that the experiment actually excluded.

For an integrated mechanism, the strongest record follows material or information across the proposed bridge. It shows the upstream event, the intermediate dependency and the downstream consequence under interventions that separate them. If one step remains unmeasured, that step should remain visible as a hypothesis. The aim is a paper whose strongest conclusion is also the conclusion a reader can reconstruct from the evidence.

References and Source Notes

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