

From mitochondria to innate immunity: The mtDNA-driven cGAS/STING-NLRP3 cascade and its therapeutic implications in neurodegenerative diseases (Review)

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Abstract. Neurodegenerative diseases (NDDs) are commonly accompanied by persistent low-grade neuroinflammation, yet current therapies rarely achieve durable disease modification. This review aims to systematically delineate the role of mitochondrial DNA (mtDNA) leakage in linking mitochondrial injury to innate immune activation and to explore its pathological significance in NDDs. A comprehensive review of recent literature on mitochondrial stress, mtDNA release and innate immune signaling was conducted. Evidence was integrated regarding the sources of mtDNA immunogenicity, routes of mtDNA escape, mitophagy-lysosome gating mechanisms and the modulation of leakage baseline by aging and metabolic stress. Accumulating evidence indicates that cytosolic mtDNA is sensed by cyclic GMP-AMP synthase (cGAS) and activates the stimulator of interferon (IFN) genes (STING) pathway signaling through the TANK-binding kinase 1 and IFN regulatory factor 3 axis to induce type I IFN responses and promoting NF- κ B-driven inflammatory transcription, thereby enhancing NLRP3 inflammasome priming. Oxidized mtDNA, pore-forming membrane events and ionic imbalance further facilitate NLRP3 assembly and pyroptotic execution, exacerbating mitochondrial damage

and mtDNA release in a self-amplifying loop. Based on these findings, a modular assessment framework was proposed across the 'input-chronicity-amplification' layers and the potential of mtDNA-cGAS/STING-NLRP3 axis-informed stratified diagnosis and treatment was discussed. Central nervous system-targeted delivery, cellular heterogeneity and immune safety windows remain critical for translational research. This review provides a testable mechanistic framework and a clinical evaluation pathway for understanding mtDNA-driven persistent inflammation in NDDs.

Contents

1. Introduction
2. Sources and determinants of mtDNA leakage
3. mtDNA activates cGAS/STING: The chronicity module
4. mtDNA and the NLRP3 inflammasome: The amplification module
5. The cGAS/STING-NLRP3 feed-forward circuit
6. From mechanism to translation: stratified interventions along the mtDNA-cGAS/STING-NLRP3 axis
7. Discussion

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Abbreviations: mtDNA, mitochondrial DNA; cGAS, cyclic GMP-AMP synthase; STING, stimulator of IFN genes; TBK1, TANK-binding kinase 1; IRF3, IFN regulatory factor 3; IFN-I, type I interferon; NF- κ B, nuclear factor κ B; NLRP3, NOD-like receptor family pyrin domain containing 3

Key words: mtDNA, cGAS/STING, NLRP3 inflammasome, neuroinflammation, stratified assessment

1. Introduction

Neurodegenerative diseases (NDDs) are characterized by progressive neuronal loss and include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) (1). These disorders are closely associated with cognitive decline, motor dysfunction, synaptic loss and neuronal death, and the accumulation and spread of pathological proteins through neural circuits often parallels disease progression (2). In recent years, the global prevalence and burden of neurological diseases have continued to rise, further increasing the long-term care pressure imposed by NDDs (3,4). Although multiple pharmacological and multimodal interventions have been developed, most current treatments are aimed at symptomatic relief or modest slowing of progression and rarely interrupt the persistent pathological

processes at their roots. Traditional views emphasize aberrant aggregation of proteins such as amyloid- β (A β), α -synuclein (α -syn) and tau as key drivers (5-8). However, growing evidence indicates that protein pathology alone is insufficient to account for the full disease trajectory (9). Therefore, identifying the key mechanisms that bridge diverse pathological stimuli and translating them into actionable interventions remains a major priority.

An increasing body of evidence suggests that numerous NDDs are not single-line events driven solely by protein abnormalities, but instead reflect long-term remodeling that integrates organelle stress with innate immune responses (10-12). Among mitochondrial alterations, mitochondrial DNA (mtDNA) deserves particular attention: It retains bacteria-like molecular features and is readily oxidized under stress, thereby acquiring potent immunostimulatory capacity and acting as a key trigger of inflammatory signaling (13-15). When mitochondria undergo oxidative stress, altered membrane permeability or impaired quality control, short mtDNA fragments can escape into the cytosol via voltage-dependent anion channel (VDAC) pathways and subsequently elicit type I interferon (IFN-I)-related responses; notably, this can occur in living cells (13,16). In addition, oxidized DNA fragments can exit through mitochondrial permeability transition pore (mPTP)- and VDAC-associated routes and, within the same cellular context, simultaneously engage IFN signaling and inflammasome responses, thereby linking mitochondrial injury to immune amplification in a self-perpetuating damage process (17,18).

In the central nervous system (CNS), neuroinflammation is not intrinsically detrimental: It supports clearance and repair during acute injury or infection. However, when inflammation becomes chronic and persists at low grade, it can shift into a permissive background that promotes neurodegeneration (19). Microglia are key executors of this transition. Human genetics and single-cell studies repeatedly show that AD risk genes are highly enriched in microglia and tightly linked to reactive state transitions (9). mtDNA leakage not only elevates the expression of inflammation-associated genes, but may also enhance downstream effector output by promoting assembly of the NLR family pyrin domain containing (NLRP3) inflammasome, thereby translating mitochondrial stress into an amplifiable inflammatory response (20). Furthermore, apoptosis-associated speck-like protein containing a CARD (ASC) specks generated upon inflammasome activation are not merely markers of activation; they can act extracellularly, interact with pathological proteins and promote A β oligomerization and aggregation (8), connecting mtDNA-driven inflammatory amplification to pathological protein spread-an important disease-progression event.

The cytosolic DNA-sensing pathway composed of cyclic GMP-AMP synthase (cGAS) and stimulator of IFN genes (STING) converts aberrant cytosolic DNA signals into an IFN program centered on TANK-binding kinase 1 (TBK1) and IFN regulatory factor 3 (IRF3) (21,22). In the nervous system, this pathway is widely viewed as a key mechanism that sustains sterile neuroinflammation and it is among the best-supported downstream response axes following mitochondrial stress-induced mtDNA leakage (23). Increasing evidence suggests that the cGAS/STING pathway and the

NLRP3 inflammasome are not independent; rather, they can be co-engaged under shared cellular stress and amplify each other (24). On the one hand, oxidized DNA fragments can escape through mitochondria-associated routes and, within the same cellular system, concurrently trigger IFN signaling and inflammasome activation, providing a direct mechanistic basis for parallel initiation of the two pathways (18). On the other hand, membrane events associated with cell death can increase cytosolic exposure of mtDNA, amplifying cGAS/STING-driven IFN responses, while inflammasome amplification further injures mitochondria and increases the probability of additional DNA release-together favoring signal persistence (23). Accordingly, this review proposes to stratify pathological contexts based on circuit activity to better match intervention strategies.

Over the past decade, the understanding of innate immunity in maintaining immune homeostasis and driving chronic inflammation has deepened substantially, particularly regarding the cGAS/STING pathway, inflammasomes and pyroptosis (Fig. 1). Although these modules are defined as relatively distinct in classical terms, they often form tightly coupled networks in cells through shared stress signals and feed-forward amplification, jointly shaping sustained immune activation across diverse inflammatory diseases. Centering on mtDNA escape as an upstream event, this review systematically summarizes how mtDNA leakage engages cGAS/STING and the NLRP3 inflammasome and promotes their coupling, highlighting key molecular mechanisms and control nodes across pathological contexts. Furthermore, interaction patterns were synthesized within this coupled network and therapeutic strategies and translational implications were discussed with the goal of providing a clearer framework for mechanistic and therapeutic exploration of neuroinflammation-associated NDDs.

2. Sources and determinants of mtDNA leakage

Biological features and immunogenicity of mtDNA. The immunogenicity of mtDNA arises first from its molecular features and intracellular organization. mtDNA retains bacteria-like sequence and structural properties and exists as circular double-stranded DNA (25). Thus, once it appears in an inappropriate compartment, it is readily interpreted as a danger signal. Moreover, mtDNA is typically packaged into nucleoids and stably bound by proteins such as TFAM. Therefore, when nucleoid homeostasis is disrupted, cytosolic mtDNA increases, indicating that nucleoid integrity can itself determine whether mtDNA becomes available for sensing (13,26).

The immune effects of mtDNA are closely linked to the extent of oxidative modification and to the form of the fragments that enter the cytosol. Under oxidative stress, ox-mtDNA can, in primed cells, promote NLRP3-associated responses and enhance maturation and release of IL-1 β , whereas reducing ROS or limiting mtDNA oxidation attenuates inflammasome output (20). In parallel, oligomerization of VDAC creates pores in the outer mitochondrial membrane that enable the release of short mtDNA fragments; the inhibitor VBIT-4 reduces cytosolic mtDNA and downstream IFN-I levels and alleviates lupus-like disease (16). Human and *in vivo* studies further indicate that release of ox-mtDNA nucleoids can

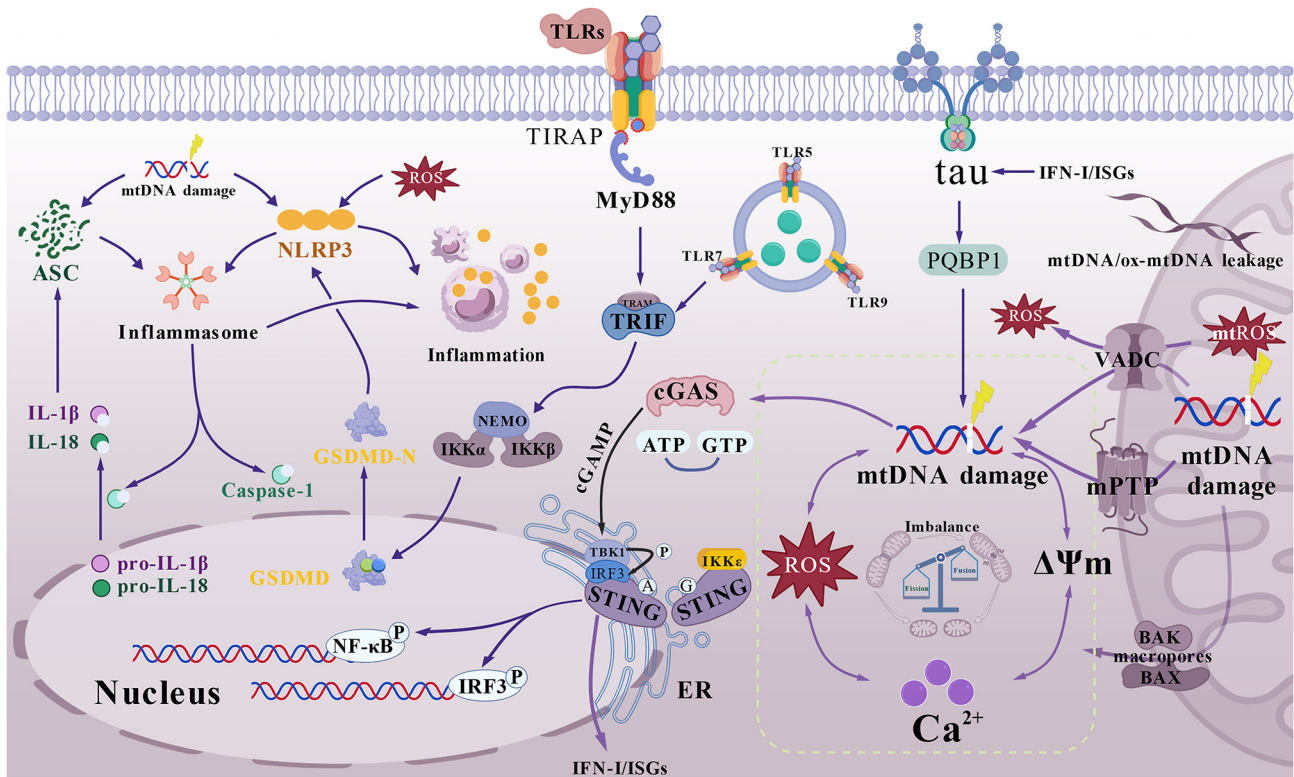


Figure 1. Overview of the mtDNA leakage-driven cGAS/STING-NLRP3 feed-forward circuit in neuroinflammation and NDDs. Mitochondrial stress promotes mtDNA [including oxidized mtDNA (ox-mtDNA)] release into the cytosol, enabling cytosolic DNA sensing by cGAS and downstream STING activation. Activated STING can signal through TBK1-IRF3 to induce type I IFN programs, and can also bias toward NF- κ B-dominant inflammatory transcription, thereby enhancing inflammasome priming. In parallel, mtDNA-associated mitochondrial danger signals facilitate NLRP3 inflammasome assembly, caspase-1 activation, and downstream cytokine maturation and pyroptotic execution. Inflammasome-driven membrane events and mitochondrial injury further increase mtDNA availability, forming a self-amplifying loop that sustains neuroinflammation and accelerates neurodegenerative progression. mtDNA, mitochondrial DNA; ROS, reactive oxygen species. A, adenosine; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; ATP, adenosine triphosphate; Ca^{2+} , calcium ion; cGAMP, cyclic guanosine monophosphate-adenosine monophosphate; cGAS, cyclic guanosine monophosphate-adenosine monophosphate synthase; DNA, deoxyribonucleic acid; $\Delta\Psi$ m, mitochondrial membrane potential; ER, endoplasmic reticulum; G, guanosine; GSDMD, gasdermin D; GSDMD-N, N-terminal fragment of gasdermin D; GTP, guanosine triphosphate; IFN, interferon; $\text{IKK}\alpha$, inhibitor of NF- κ B kinase subunit α ; IRF3, interferon regulatory factor 3; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; MyD88, myeloid differentiation primary response 88; NDDs, neurodegenerative diseases; NEMO, NF- κ B essential modulator; NF- κ B, nuclear factor κ B; NLRP3, nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing protein 3; ox-mtDNA, oxidized mitochondrial DNA; P, phosphorylation; PQBP1, polyglutamine-binding protein 1; pro-IL-1 β , precursor interleukin-1 β ; ROS, reactive oxygen species; STING, stimulator of interferon genes; tau, microtubule-associated protein tau; TBK1, TANK-binding kinase 1; TIRAP, Toll/IL-1 receptor domain-containing adaptor protein; TLRs, Toll-like receptors; TRAM, TRIF-related adaptor molecule; TRIF, Toll/IL-1 receptor domain-containing adaptor-inducing IFN- β .

strengthen IFN-I phenotypes, and extracellular mtDNA can also amplify inflammation via endosomal Toll-like receptor (TLR)9, highlighting a cross-compartment immunodriver role for mtDNA (27,28).

mtDNA immunogenicity is not confined to settings of overt acute injury; metabolic stress can likewise lower the threshold for mtDNA sensing (29,30). In a pyrimidine-depletion model, metabolic imbalance induced cytosolic mtDNA accumulation and drove TBK1/IRF3 signaling with upregulation of IFN-stimulated genes (ISGs). Correcting the metabolic constraint or targeting key nodes reversed these readouts, indicating that metabolic state can reset the background permissiveness for mtDNA sensing (31).

Routes of mtDNA escape. Multiple routes can mediate mtDNA escape, occurring under stress in viable cells and becoming markedly amplified during cell death (32,33). At the outer membrane, VDAC oligomerization forms pores that release short mtDNA fragments; inhibiting this process lowers

cytosolic mtDNA and IFN-I-related readouts, indicating that outer-membrane channels alone can drive leakage (16). At the inner membrane, mPTP-associated pore events facilitate escape of oxidized DNA fragments and can, within the same system, activate IFN-I and NLRP3-related responses in parallel (18). During MOMP, large pores formed by BCL2-associated X protein (BAX) and BCL2 antagonist/killer 1 (BAK) can induce inner-membrane herniation and allow matrix components (including mtDNA) to enter the cytosol (34). Under caspase-restricted conditions, mtDNA-driven cGAS/STING signaling becomes particularly prominent (35). In addition, mitochondrial-derived vesicles and the endosome/lysosome axis can traffic mitochondrial cargo under milder conditions, and insufficient lysosomal disposal favors mtDNA accumulation (36). Mechanisms dependent on PTEN-induced kinase 1 (PINK1) can also promote loading of mtDNA into extracellular vesicles (EVs) and induce inflammatory phenotypes in recipient cells (29). Overall, the route of escape shapes the source compartment, fragment form and supply rate of

mtDNA, thereby tuning cellular sensitivity to mtDNA and the initiation and persistence of inflammatory responses.

Mitophagy and lysosomal gating. Mitophagy is the selective removal of damaged mitochondria through the autophagy-lysosome system (37). Its key protective value lies in eliminating dysfunctional mitochondria in time, thereby reducing mtDNA at its source. A drop in mitochondrial membrane potential ($\Delta\psi_m$) stabilizes PINK1 on the outer membrane and initiates a Parkin-mediated ubiquitination cascade, which subsequently recruits receptors and autophagy machinery to engulf and clear damaged mitochondria (38–40). This process is reproducible across multiple cell systems and can be quantified by readouts such as Parkin recruitment, outer-membrane ubiquitination and light chain 3 (LC3) assembly. In neuron-relevant settings, Parkin-mediated mitochondrial quality control (MQC) is also linked to stress outcomes, supporting a gating role of this axis in high-energy-demand cells (41,42).

BCL2/adenovirus E1B 19 kDa-interacting protein 3-like (BNIP3L; also known as NIX) is an outer-mitochondrial-membrane receptor protein. Under hypoxia or metabolic stress, both BNIP3 and NIX/BNIP3L can recruit LC3/GABARAP via their LC3-interacting region (LIR) motifs to promote clearance of damaged mitochondria. Loss of NIX impairs mitochondrial clearance and leads to detectable mitochondrial retention (43,44). Evidence shows that NIX/BNIP3L interacts with LC3/GABARAP through its LIR motif to support selective mitophagy (43). During hypoxia or metabolic stress, BNIP3 upregulation can drive mitophagy and help reduce reactive oxygen species (ROS)-associated oxidative burden, accelerating removal of injured mitochondria (45). Recent work further indicates that under hypoxic conditions, ROS-driven hypoxia-inducible factor-1 α /BNIP3/NIX-mediated mitophagy can reduce cytosolic mtDNA-linked inflammation and attenuate apoptosis, thereby improving cellular function (46).

Importantly, whether mitophagy truly lowers the risk of mtDNA leakage ultimately depends on lysosomal disposal capacity (37). In models with neuronal DNase II deficiency or microglia-specific knockdown of DNase2a, cytosolic double-stranded DNA accumulates, pro-inflammatory mediators increase and neuroinflammatory/neurodegenerative phenotypes worsen—more directly illustrating the importance of lysosomal nucleic-acid clearance (47). A recent study also suggest that in aged mice, weakened mitophagy and mtDNA accumulation enhance inflammation, whereas urolithin A-induced mitophagy suppresses mtDNA-driven inflammatory readouts (38). Collectively, mitophagy reduces mtDNA accumulation and leakage by removing damaged mitochondria in a timely manner and completing disposal through lysosomes, thereby mitigating mtDNA-associated inflammation (Fig. 2).

Aging and metabolic stress reset the leakage baseline. With aging, cells are more prone to persistent mitochondrial perturbations and a background of low-grade inflammation (48,49). In the aged mouse brain, Gulen *et al* (24) observed microglia with a more reactive transcriptional state accompanied by neurodegeneration and cognitive decline, suggesting that aging itself can set the immune system toward a configuration that is more readily and persistently activated. Furthermore,

in acute metabolic-stress paradigms, ischemia-reperfusion or oxygen-glucose deprivation/reperfusion (OGD/R) increases neuronal ox-mtDNA and activates cGAS/STING, whereas limiting ox-mtDNA escape reduces inflammation and improves neurological function—indicating that metabolic disturbance can rapidly lower the threshold for mtDNA sensing (50).

Aging is also frequently accompanied by diminished mitophagy, making damaged mitochondria harder to clear and thereby increasing the likelihood of mtDNA accumulation and escape (51,52). In aged macrophage models, hypoxia/reoxygenation stress led to impaired mitophagy, enhanced mitochondrial injury and ROS, and a more pronounced rise in cytosolic mtDNA; restoring mitophagy reduced cytosolic mtDNA and dampened inflammation (53). In addition, declining mtDNA repair capacity can accumulate mtDNA damage and instability, increasing leakage probability and lowering the threshold for inflammatory triggering upon aberrant mtDNA localization (54,55). In transgenic mice and cell models with mitochondrial-targeted 8-oxoguanine DNA glycosylase (OGG1), higher mtOGG1 levels reduced age-associated inflammatory factors and neuroinflammation (56). Consistently, defects in mitochondrial topoisomerase-related genes can also facilitate mtDNA entry into the cytosol and provoke inflammatory responses in cellular systems. Together, these findings indicate that disruption of mitochondrial nucleic-acid metabolism that maintains mtDNA homeostasis can likewise lower the leakage threshold and promote inflammation (57).

3. mtDNA activates cGAS/STING: The chronicity module

mtDNA triggers cGAS/STING signaling. Following mitochondrial injury, mtDNA more readily enters the cytosol, activating cGAS and downstream STING signaling through TBK1 and IRF3, culminating in elevated IFN-I and ISGs alongside aggravated neuroinflammation (21,58). In ischemia-related models, Kong *et al* (59) observed concordant increases in mtDNA-linked signals and STING activation after middle cerebral artery occlusion, with microglia skewing toward a pro-inflammatory state; STING inhibition reduced inflammation and markedly improved outcomes. In traumatic brain injury models, activation of the cGAS/STING axis is likewise detected after injury, together with enhanced IFN-I and inflammatory responses, and these changes are more pronounced in aged settings (60).

More direct evidence comes from experiments that causally link mtDNA status to cGAS/STING activation. Li *et al* (50) reported that in rat ischemia-reperfusion and neuronal OGD/R models, ox-mtDNA increased and activated cGAS/STING, supporting ox-mtDNA as an upstream input for this pathway. In microglia models with metabolic/lysosomal burden, mtDNA was also more readily released into the cytosol, accompanied by upregulated STING signaling and an amplified inflammatory phenotype, indicating that mitochondrial stress can be converted into sustained inflammatory drive within immune cells (61).

Animal studies across disease contexts further suggest that this axis is not only upregulated but also actionable. In a cerebral venous sinus thrombosis model, elevation of the cGAS/STING

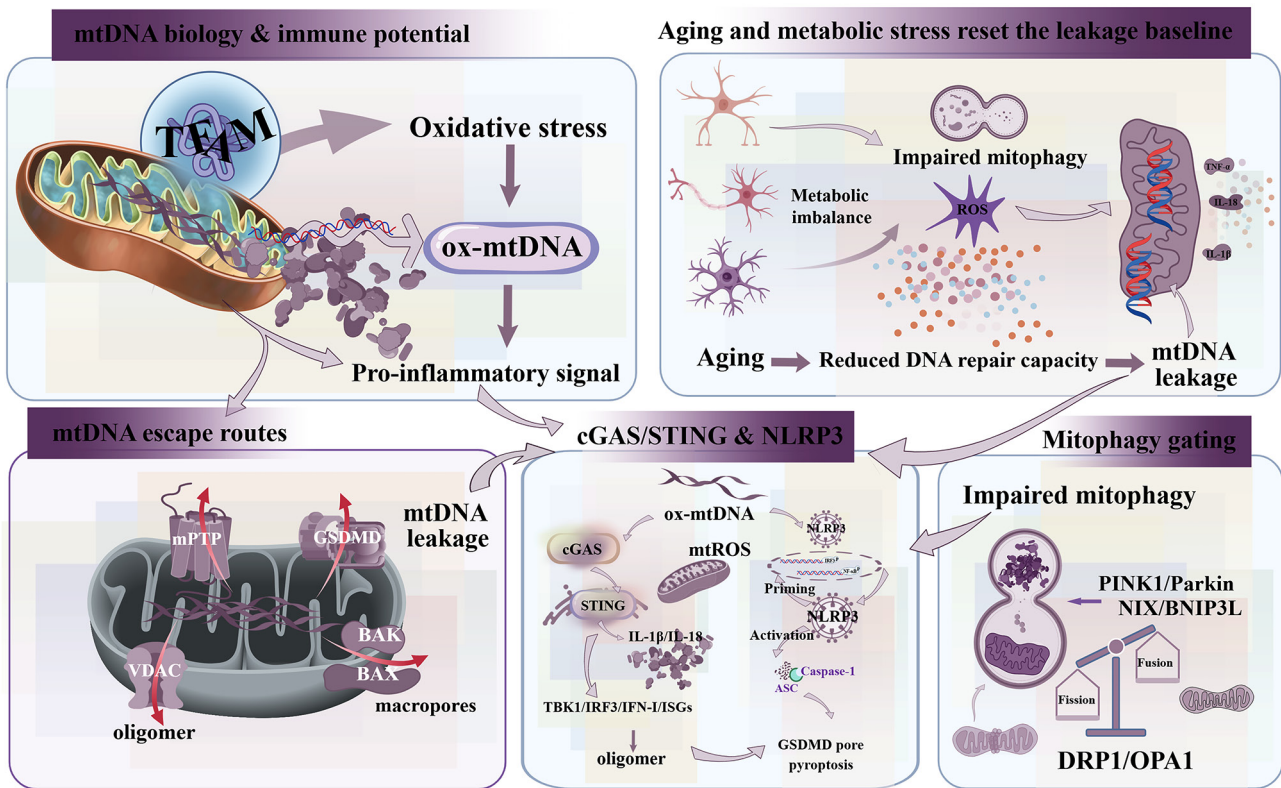


Figure 2. Determinants of mtDNA leakage and its coupling to cGAS/STING and NLRP3 signaling. Schematic summary of the major factors that shape mtDNA immunostimulatory potential and govern its release. mtDNA is normally packaged into nucleoids stabilized by TFAM; oxidative stress promotes the generation of ox-mtDNA, increasing its inflammatory potency. Multiple escape routes mediate mtDNA leakage under stress or death-related conditions, including VDAC oligomerization at the outer membrane, mPTP-associated inner-membrane events and BAX/BAK macropore-driven inner-membrane herniation; pore-forming executors such as GSDMD can further facilitate release during pyroptosis. Cytosolic mtDNA/ox-mtDNA engages cGAS/STING signaling to induce TBK1/IRF3-dependent type I IFN programs and enhances priming for NLRP3 inflammasome activation, which culminates in caspase-1 activation, ASC speck formation, cytokine maturation and GSDMD pore-mediated pyroptosis. Mitophagy-lysosome pathways dependent on PINK1/Parkin and NIX/BNIP3 gate mtDNA availability by clearing damaged mitochondria, while aging and metabolic stress reset the leakage baseline via impaired mitophagy, elevated ROS and reduced DNA repair capacity. ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; BAK, B-cell lymphoma 2 antagonist/killer 1; BAX, B-cell lymphoma 2-associated X protein; BNIP3, B-cell lymphoma 2-interacting protein 3; caspase-1, cysteine-aspartic protease 1; cGAS, cyclic guanosine monophosphate-adenosine monophosphate synthase; DNA, deoxyribonucleic acid; DRP1, dynamin-related protein 1; GSDMD, gasdermin D; IFN-I, type I interferon; IL-1β, interleukin-1β; IRF3, interferon regulatory factor 3; ISGs, interferon-stimulated genes; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; NIX, B-cell lymphoma 2-interacting protein 3-like protein; NLRP3, NLR family pyrin domain-containing protein 3; OPA1, optic atrophy 1; ox-mtDNA, oxidized mitochondrial DNA; PINK1, phosphatase and tensin homolog-induced kinase 1; ROS, reactive oxygen species; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; TFAM, mitochondrial transcription factor A; VDAC, voltage-dependent anion channel.

axis correlated with worsened neuroinflammation, and targeting the axis alleviated pathology alongside reductions in microglia-associated inflammatory phenotypes (62). These findings align with observations in cGAS gain-of-function mouse models (24). Together, they support the concept that mtDNA transfer from mitochondria to the cytosol can convert mitochondrial stress into a cGAS/STING-mediated IFN-I milieu, providing sustained propulsion for inflammatory chronicity.

Requirements for cGAS activation and mtDNA immunogenicity. Whether mtDNA activates cGAS depends first on whether mtDNA reaches the cytosol and becomes spatially accessible to cGAS. Multiple live-cell studies show that mitochondria can release mtDNA into the cytosol under oxidative or metabolic stress, followed by enhanced downstream STING signaling and induction of IFN-I programs—indicating that relocalization alone can convert mitochondrial stress into immune signaling (13,16,46). Second, the modification state of mtDNA

strongly influences activation strength, with ox-mtDNA being the most representative example (38). Consistently in immune cells, oxidized DNA fragments can enter the cytosol through mitochondria-associated routes and activate cGAS/STING while promoting pro-inflammatory responses, suggesting that oxidation affects not only magnitude but also persistence of responses (18).

The physical form in which mtDNA appears is also critical. Certain studies observed that short mtDNA fragments can reach the cytosol via VDAC and drive cGAS/STING responses, whereas stronger membrane-disruptive events that remodel mitochondrial architecture can deliver more matrix content together with mtDNA into the cytosol, more readily establishing a sustained IFN-I increase (16,62–65). Thus, mtDNA-driven cGAS activation reflects the integration of multiple conditions: Spatial accessibility determines contact, oxidative modification determines stimulus potency, and fragment form and supply route influence whether the signal is prolonged into a chronic background (Fig. 3).

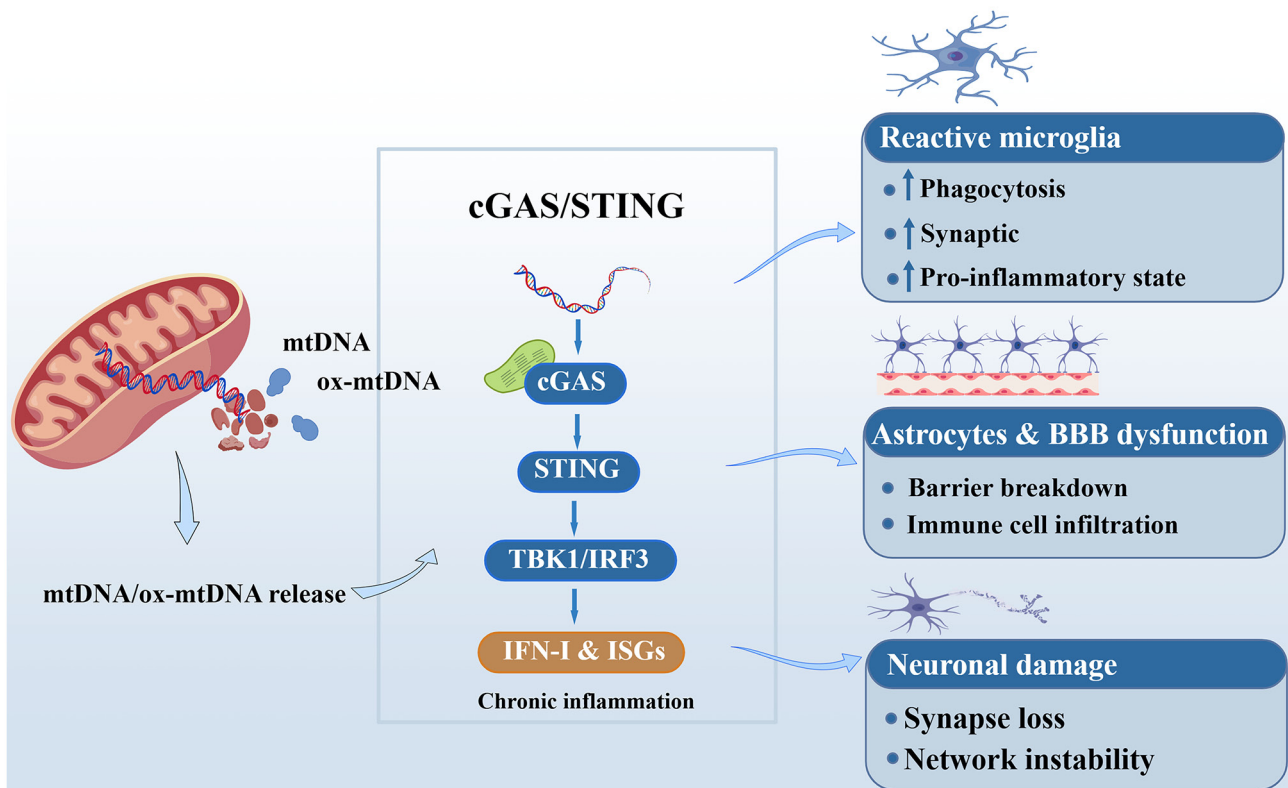


Figure 3. mtDNA-triggered cGAS/STING signaling as a chronicity module shaping CNS cellular states. Cytosolic mtDNA activates the cGAS/STING axis and drives IFN-I production and ISG expression, thereby remodeling microglial reactivity, promoting astrocytic responses, and impairing BBB integrity. These coordinated changes increase synaptic vulnerability and neuronal dysfunction, providing a mechanistic route through which mtDNA stress contributes to persistent neuroinflammatory states in NDDs. BBB, blood-brain barrier; cGAS, cyclic GMP-AMP synthase; CNS, central nervous system; IFN-I, type I interferon; IRF3, interferon regulatory factor 3; ISGs, interferon-stimulated genes; NDDs, neurodegenerative diseases; ox-mtDNA, oxidized mitochondrial DNA; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; ↑, increased.

IFN-I reshapes CNS cellular states. In microglia, IFN-I often pushes cells toward a more reactive state, characterized by sustained elevation of ISGs, upregulation of phagocytic and complement-related genes and an increased tendency toward excessive processing of synaptic structures. Roy *et al* (66) observed ISG-positive microglia clustering around plaques in multiple A β mouse models and in human brain material, and demonstrated that blocking IFN-I signaling reduced microglial activation and improved synapse loss. The same group further showed that A β can induce a broad brain-wide IFN-I response and coordinated IFN-I-related transcriptional changes across multiple cell types, accompanying cognitive decline (67). Consistently, in amyloid precursor protein/presenilin 1 (APP/PS1) and related models, genetic removal of IFN- α and - β receptor subunit 1 altered microglial responses to A β and phagocytic phenotypes, supporting IFN-I as a key driver of microglial state transitions (68). In human induced pluripotent stem cell-derived microglia systems, persistent IFN-I signaling has also been linked to microglial dysfunction and senescence-like changes, with secondary impacts on neuronal synaptic function (69).

In astrocytes and at the blood-brain barrier (BBB), IFN-I effects are often not confined to a single node but can trigger secondary amplification. Astrocytic IFNAR signaling can alter BBB permeability and influence the degree of inflammatory-cell entry into the CNS, with clear *in vivo* evidence from infectious encephalitis models (70). In AD-relevant contexts, IFN-I signaling

has likewise been reported to accompany changes in endothelial barrier function, suggesting a role in establishing or maintaining BBB fragility (71). In addition, recent work has begun to identify astrocyte subpopulations associated with IFN-regulatory factors in disease samples and link them to inflammatory severity, implying that IFN-I may shape the long-term inflammatory milieu through astrocytic programs (72).

Ultimately, these changes converge on synaptic homeostasis and network vulnerability. IFN-I can enhance complement-related pathways, enabling microglia to more readily participate in synaptic removal and contributing to declines in synapse number and function. This has been directly demonstrated in the AD models described above, where IFN blockade partially restored synapses and behavioral performance (66). Complement-microglia-driven synapse loss is not limited to AD; stress-related models also show spatially selective synaptic reductions, suggesting that once the complement axis is elevated, neural circuits become more fragile (73). Therefore, persistent IFN-I/ISG elevation often indicates a CNS environment in which immune cells more readily adopt hyper-reactive states, glial and BBB secondary responses are amplified and synaptic homeostasis becomes harder to maintain-together favoring a chronically inflamed milieu.

Integrating disease-relevant evidence. In AD-related models, cGAS/STING- and IFN-I-associated changes often accompany enhanced microglial reactivity. In one AD model,

STING activation exacerbated microglial dysfunction and inflammation, whereas STING inhibition alleviated multiple pathological and behavioral phenotypes, supporting the actionability of this axis (74). Evidence linked to risk factors points in the same direction: Carling *et al* (75) analyzed microglial changes in the context of AD risk alleles and reported associations between cGAS/STING signaling and senescence-like microglial states that may contribute to disease susceptibility.

In PD research, the evidence appears more model-dependent. The Standaert group reported that misfolded α -syn can induce DNA damage in microglia and activate cGAS/STING-mediated inflammation, thereby promoting neurodegeneration (76). However, in an α -syn preformed fibril mouse model, loss of functional STING altered immune responses but did not necessarily confer dopaminergic neuroprotection, indicating that PD contexts require finer dissection by model stage and cell type (77).

In tauopathies, evidence for pathway upregulation and benefit from blockade are more consistent. In tauopathy mice and human brain samples, microglial cGAS/IFN programs were activated; genetic deletion of cGAS protected synapses and cognitive function and was associated with improved microglial transcriptional networks (78). In addition, IFN-I responses have been reported to promote seeded tau aggregation, suggesting that IFN-I may be a key factor that facilitates tau pathology expansion (79).

In aging, the link between this axis and neuroinflammatory persistence is even more direct. STING activation drives microglia toward reactive transcriptional states and is associated with neurodegeneration and cognitive decline; blocking STING reduces brain inflammation and improves tissue function, indicating that aging itself can elevate this pathway (24). Nevertheless, a recent study has also proposed that STING may exert protective roles in maintaining brain homeostasis, suggesting that its effects may depend on stimulus strength, duration, and cell type (80).

Taken together, across AD, PD, tauopathies and aging, cGAS/STING-related signaling frequently parallels increased reactivity of CNS immune cells. Intervening on this axis alleviates inflammation and improves selected functional outcomes in multiple models, supporting a role in sustaining neuroinflammation and driving disease progression.

4. mtDNA and the NLRP3 inflammasome: The amplification module

Two-step activation: Priming and activation. NLRP3 inflammasome activation typically requires two steps. The first is priming, in which transcriptional pathways such as NF- κ B increase expression of NLRP3 and precursors such as pro-IL-1 β and pro-IL-18 and shift cells into a more activation-permissive state. Recent studies commonly use priming stimuli such as lipopolysaccharides, TNF- α or IL-1 β to induce NLRP3 and pro-IL-1 β expression (81-84). Conversely, blocking NF- κ B or disrupting key transcriptional regulation can prevent IL-1 β maturation and release even in the presence of strong downstream stimuli (85,86).

The second step is activation, which is typically accompanied by intracellular danger-signal changes, such as K⁺ efflux, increased mitochondrial ROS, lysosomal damage or

disrupted Ca²⁺ homeostasis (87,88). After priming, a key event is NLRP3 assembly with ASC and recruitment of caspase-1. ASC, encoded by PYD and CARD domain containing, connects to NLRP3 via PYD and recruits pro-caspase-1 via CARD, enabling autocleavage and generation of active caspase-1 within the complex (89). ATP can promote NLRP3 activation through P2X7-mediated K⁺ efflux, and blocking K⁺ efflux reduces inflammasome output (90). Likewise, lysosomal rupture triggered by crystals or aggregates can activate NLRP3, while stabilizing lysosomes reduces IL-1 β release (69,70). NIMA related kinase 7 (NEK7) is an important factor for NLRP3 activation; NEK7 deficiency impairs NLRP3 activation, underscoring the need for specific intracellular assembly conditions (91). Once caspase-1 is activated, the most direct consequence is maturation of pro-inflammatory cytokines, which amplifies local inflammation and alters neighboring cell states. Pharmacological inhibition of NLRP3 can also suppress ASC/caspase-1-dependent outputs and alleviate inflammation (92).

Gasdermin D (GSDMD) is the terminal executor of pyroptosis (93). Caspase-1 cleaves GSDMD to release the N-terminal fragment, which forms pores in the plasma membrane, leading to leakage of cellular contents and pyroptotic cell death (94,95). The pore-forming and pyroptotic function of GSDMD has been validated in multiple key experiments; GSDMD deficiency markedly weakens pyroptosis and reduces IL-1 β release (36). Accordingly, pyroptosis-related signaling tightly correlates with inflammatory severity, and GSDMD often determines the magnitude and spread of neuroinflammatory output.

Mitochondrial stress is often an important source of activation signals. Experimental evidence indicates that increased mtROS, altered mitochondrial membrane potential and mtDNA/ox-mtDNA mislocalization are key contributors to NLRP3 assembly and enhanced maturation and release of IL-1 β (20). Conversely, reducing mitochondrial ROS or limiting mtDNA oxidation diminishes inflammasome output. In sum, the NLRP3 inflammasome is typically primed by NF- κ B-dependent upregulation of core components and then activated to assemble the complex and activate caspase-1, ultimately driving maturation and release of IL-1 β and IL-18 (Fig. 4).

How mtDNA contributes to NLRP3 activation. mtDNA involvement in NLRP3 activation typically follows mitochondrial stress. Cellular and animal systems show that oxidized DNA fragments generated in mitochondria can be processed by flap structure-specific endonuclease 1 into smaller fragments and escape into the cytosol via mPTP- and VDAC-associated routes (18,96,97). Once in the cytosol, these fragments promote NLRP3-related responses and increase inflammatory outputs such as IL-1 β (98,99). Importantly, evidence indicates that mtDNA is not merely a background signal: Measurable physical interactions exist between NLRP3 and mtDNA. Cabral *et al* (100) directly observed NLRP3 binding to mtDNA *in vitro* and found distinct binding characteristics for mtDNA with different oxidation states, providing mechanistic support for mtDNA as a direct participant in the NLRP3 activation process. Although mtDNA-NLRP3 binding may be relatively transient, it can regulate the activation threshold under conditions of mtDNA accumulation or oxidation, while

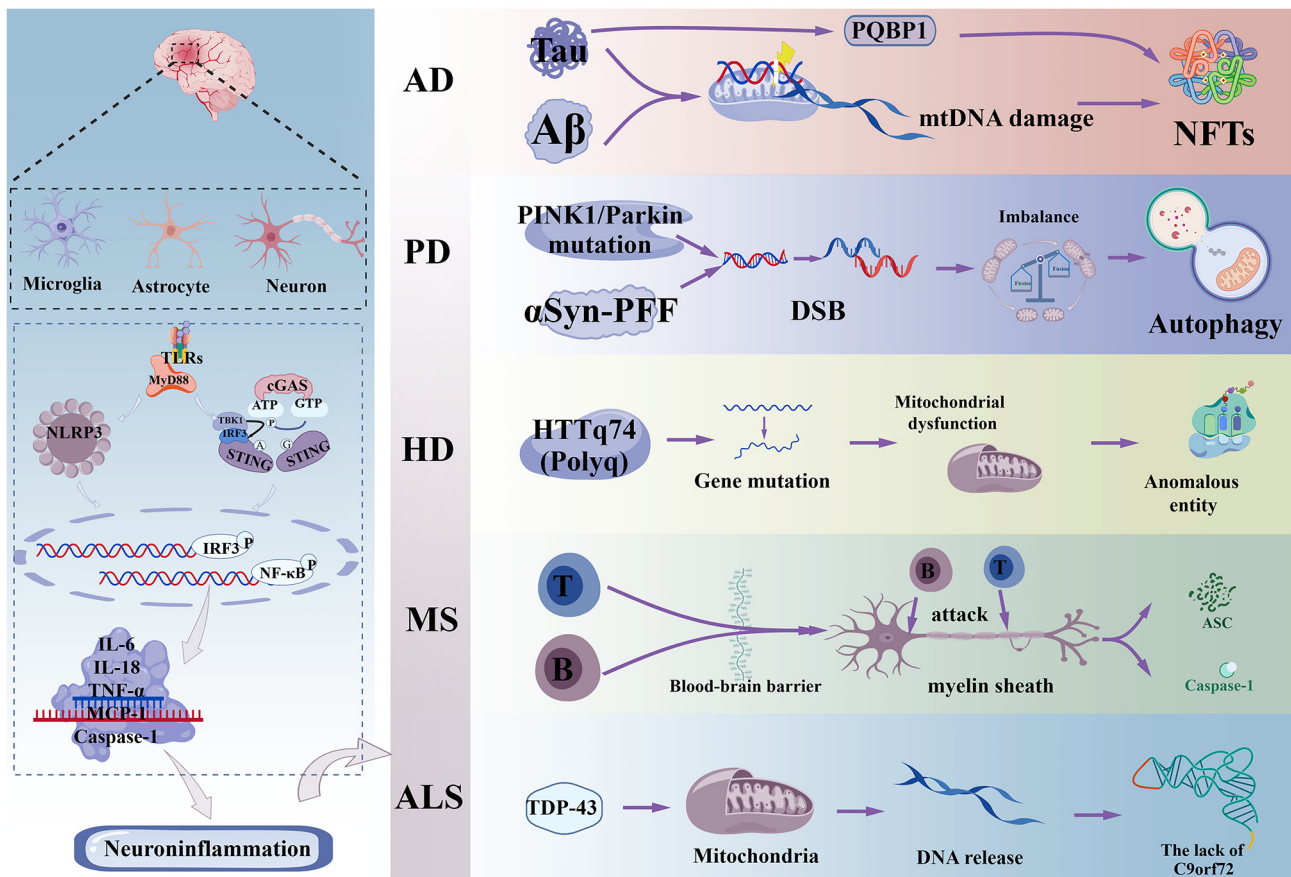


Figure 4. mtDNA-associated NLRP3 inflammasome activation and pyroptotic amplification module. Mitochondrial dysfunction and membrane permeability changes increase cytosolic exposure of mtDNA and related danger signals, facilitating NLRP3 inflammasome assembly and downstream caspase-1 activation. Inflammasome activation promotes inflammatory mediator release and pyroptotic execution, which propagates danger signals to neighboring cells and further aggravates mitochondrial stress. This amplification module provides a mechanistic basis for sustained inflammatory escalation and progressive tissue damage in NDD-related neuroinflammation. ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; mtDNA, mitochondrial DNA; NDD, neurodegenerative disease; NLRP3, NLR family pyrin domain-containing protein 3; ROS, reactive oxygen species; caspase-1, cysteine-aspartic protease 1; GSDMD, gasdermin D; GSDMD-N, N-terminal fragment of gasdermin D; IL-1 β , interleukin-1 β ; IL-18, interleukin-18; K $^{+}$, potassium ion; mtROS, mitochondrial reactive oxygen species; ox-mtDNA, oxidized mitochondrial DNA.

subsequent inflammasome assembly is stabilized by NLRP3 oligomerization and protein interactions with NEK7, ASC and pro-caspase-1 (89,91,100).

Furthermore, mtDNA effects are often amplified in concert with ROS: Rising ROS promotes mtDNA oxidation and also primes NLRP3 for assembly. In immune-cell systems, mitochondrial-surface VDAC oligomers colocalize with NLRP3 during early assembly and facilitate inflammasome formation (101). Blocking this process reduces NLRP3-dependent outputs, suggesting that the mitochondrial membrane can translate stress signals into changes in inflammasome assembly efficiency (102,103). Finally, in the extracellular space, mtDNA can indirectly amplify inflammasome responses via endosomal pathways. In hematopoietic systems, extracellular ox-mtDNA promotes inflammatory responses through the TLR9/MyD88 axis, and TLR9 inhibition or knockout supports its necessity for ox-mtDNA-induced inflammasome activation (104).

In summary, mtDNA often enters the cytosol or extracellular milieu following oxidative stress and mitochondrial membrane events. It can enhance NLRP3 assembly and output as oxidized fragments, and it can also indirectly increase the magnitude and persistence of inflammasome activation

through ROS amplification and endosomal nucleic-acid sensing.

ASC specks amplify mtDNA-linked inflammation. After mtDNA promotes NLRP3 activation, ASC can further aggregate into specks. Critically, during cell death or robust inflammatory responses, ASC specks can enter the extracellular space, extending inflammasome responses beyond a single cell to surrounding cells (105,106). Experiments show that inflammasome activation and pyroptosis release ASC specks, and extracellular specks can be taken up by neighboring immune cells to further promote inflammasome outputs, forming an amplification mechanism (107). In the nervous system, microglia-derived ASC specks can also bind pathological proteins and promote their aggregation; for example, in AD models, ASC specks bind A β and promote A β oligomerization and aggregation (8), and targeting ASC reduces related pathology and inflammation (108,109). These findings indicate that mtDNA-induced inflammasome activation not only elevates cytokine release, but may also amplify pathology through extracellular speck propagation that facilitates deposition and spread of pathological proteins.

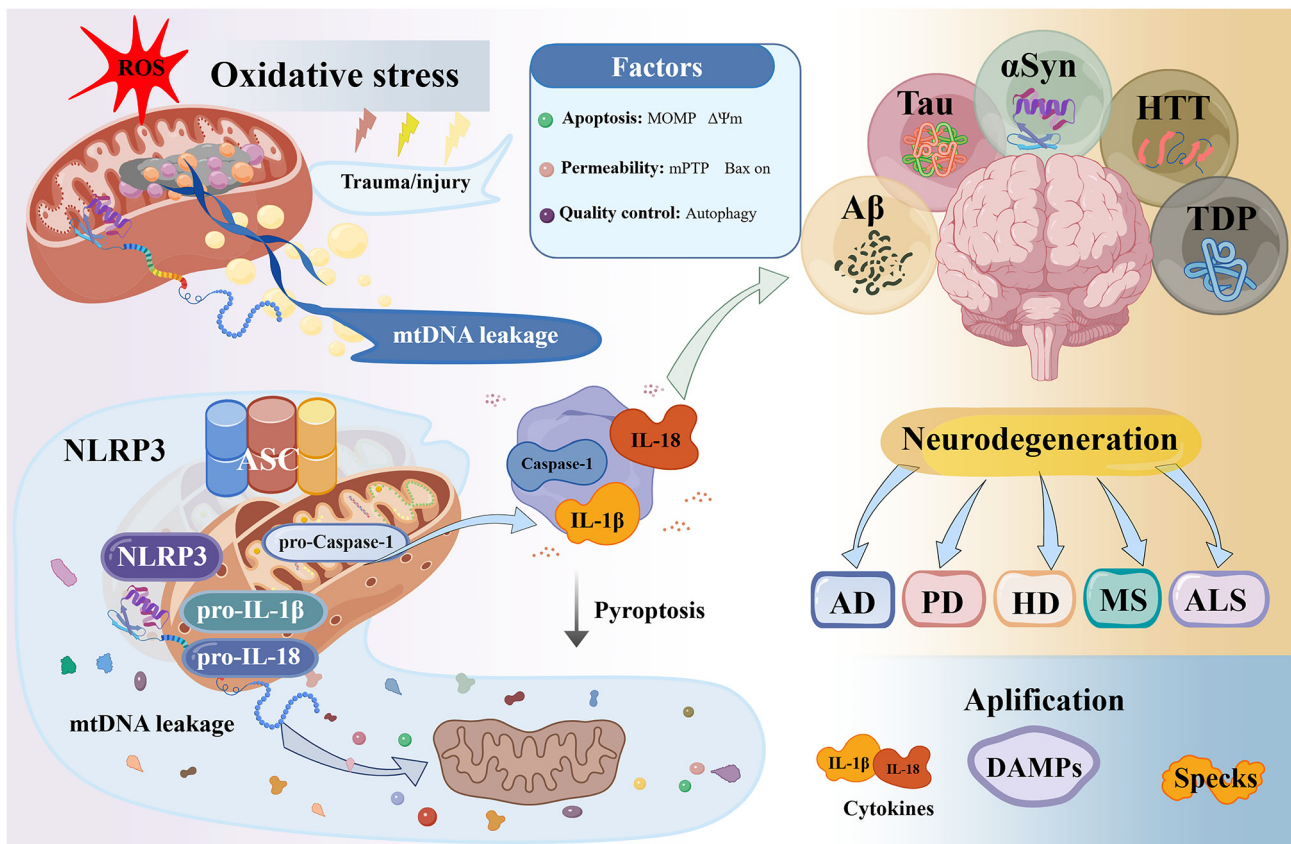


Figure 5. Cross-disease evidence map linking innate immune sensors to neurodegenerative disease-relevant triggers and outcomes. Schematic integration of representative upstream stimuli and pathological contexts across major NDDs, highlighting how innate immune sensors and downstream inflammatory modules are engaged in a disease-dependent manner. The map summarizes connections among TLR signaling, cGAS/STING activation and NLRP3 inflammasome responses in AD, PD, HD, MS and ALS, and illustrates how distinct initiating insults can converge on shared inflammatory outputs that contribute to synaptic loss and neurodegeneration. mtDNA, mitochondrial DNA; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; MS, multiple sclerosis; ALS, amyotrophic lateral sclerosis; TLR, Toll-like receptor; cGAS, cyclic GMP-AMP synthase; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; NDDs, neurodegenerative diseases; NLRP3, NLR family pyrin domain-containing protein 3; STING, stimulator of interferon genes; ROS, reactive oxygen species; pro-IL-1β, precursor interleukin-1β; Aβ, amyloid β; α-syn, α-synuclein; caspase-1, cysteine-aspartic protease 1; GSDMD, gasdermin D; IFN-I, type I interferon; IL-1β, interleukin-1β; IL-18, interleukin-18; mHTT, mutant huntingtin; NF-κB, nuclear factor κB; tau, microtubule-associated protein tau; TDP-43, TAR DNA-binding protein 43.

Integrating disease-relevant evidence. In AD, aggregation of Aβ and tau is often accompanied by enhanced NLRP3-related inflammation. Inhibiting or deleting NLRP3 or ASC reduces IL-1β output and improves selected pathological and behavioral readouts, supporting a role of inflammasomes in disease amplification (8,110). In PD, α-syn aggregation can induce microglial inflammatory responses and promote NLRP3 activation; correspondingly, genetic or pharmacological inhibition of NLRP3 alleviates inflammation and shows partial protection against dopaminergic neuronal injury (111,112). In tauopathies, inflammasome-related structural products may contribute to a permissive environment for tau propagation. Certain studies suggest that reducing inflammasome activity or blocking downstream IL-1 signaling attenuates tau-associated inflammation and improves synaptic and cognition-related outcomes (5,113), providing an experimental rationale for inhibitor-based interventions. In HD animal models, treatment with MCC950, a selective small-molecule inhibitor of the NLRP3 inflammasome, reduces inflammatory and tissue-injury indicators, and BBB- and neuron-focused results further support inflammasome involvement in HD disease amplification (114,115). In ALS models, NLRP3-related

changes emerge gradually with disease progression, while MCC950 effects on survival and inflammatory phenotypes are inconsistent, indicating notable tissue- and stage-dependent difference (116,117). As summarized in Fig. 5, disease-specific triggers across AD, PD, HD, MS, and ALS engage TLR, cGAS/STING and NLRP3 signaling to different extents but converge on shared inflammatory outputs associated with synaptic loss and neurodegeneration.

5. The cGAS/STING-NLRP3 feed-forward circuit

In this review, 'parallel' mainly refers to the branch outputs of the STING platform toward TBK1/IRF3 vs. NF-κB-driven inflammatory transcription. The term 'feed-forward circuit' refers to the sequential coupling between NF-κB-driven priming and NLRP3 assembly/pyroptotic execution, together with a positive-feedback loop in which renewed mitochondrial damage promotes additional mtDNA release.

In the context of mtDNA escape, cGAS-STING signaling not only induces IFN-I responses via the canonical TBK1-IRF3 axis, but can also route signaling toward NF-κB, effectively 'transcribing' DNA stress into an inflammatory transcriptional

program and elevating the priming requirement for NLRP3 (118). This concept is supported by animal and cellular experiments that genetically dissociate STING downstream branches: After TBK1 is recruited to STING, it not only drives IRF3 activation but also substantially determines the strength of NF- κ B activation (119,120). Beyond TBK1, inhibitor of NF- κ B kinase subunit ϵ can cooperate within the STING complex to enhance NF- κ B- and MAPK-related non-IFN responses, making STING-to-inflammatory-transcription output more plastic across cell types and stimulation conditions (121). In addition, the ubiquitin-organization mode of the STING platform contributes to selective NF- κ B output. For example, HOIL-1-interacting protein-driven M1-linked linear ubiquitin chains can create an assembly environment required for NF- κ B on STING-associated membrane signaling platforms, helping explain why IFN and NF- κ B programs can be uncoupled in certain models (122).

Conversely, once NLRP3 enters an amplification state, mitochondrial membrane events, ionic imbalance and pyroptosis-associated pore effects further increase mitochondrial stress load and promote sustained mtDNA escape, mutually amplifying inflammatory output and mitochondrial injury (123). Whether this circuit can be effectively restrained often depends on the capacity of mitophagy and lysosomal clearance, and on whether antioxidant defenses and metabolic homeostasis are sufficient to limit production and supply of ox-mtDNA (20,124,125). Furthermore, the dominant edge of the circuit may differ across NDDs: In tauopathy models, microglial NF- κ B states are tightly coupled to tau spread/toxicity, implying that inflammatory transcription can exert stronger traction on structural disease-progression events.

Overall, mtDNA leakage couples the IFN-I and NF- κ B transcriptional branches downstream of cGAS/STING and elevates NLRP3 priming, while NLRP3-driven amplification feeds back to exacerbate mitochondrial stress and further mtDNA escape. This forms a positive-feedback circuit in which ‘DNA stress-inflammatory transcription-inflammasome execution’ mutually reinforce one another, with different branches dominating across NDD models. Therefore, quantifying circuit activity and its dominant branch in specific individuals/models- and selecting combinations that cut off the input layer, suppress the chronicity layer and/or block the amplification layer-is central to translational advancement and precision intervention.

6. From mechanism to translation: Stratified interventions along the mtDNA-cGAS/STING-NLRP3 axis

Here, ‘stratification’ refers to grouping samples into interpretable and comparable stages based on the relative activity of different circuit segments, for example, combinations in which the input layer (mtDNA/ox-mtDNA supply), the chronicity layer (cGAS-STING output bias toward IFN-I vs. NF- κ B) and the amplification layer (NLRP3-pyroptosis) are each high or low.

Such stratification converts the generic question of ‘whether to anti-inflame’ into a targeted choice of ‘which module to prioritize’, improving therapeutic matching. It also helps explain discrepancies across studies and provides unified readouts for enrollment and longitudinal follow-up to establish a testable closed loop, thereby improving reproducibility and

translational value. Representative disease-level examples include tau-PQBP1-cGAS/STING signaling, microglial NF- κ B-driven tau propagation and STING-dependent α -synucleinopathy (126-128). Mitochondrial and sensing checkpoints include cristae architecture, Parkin-dependent VDAC1 ubiquitination, cytosolic TOP3 α and apoptotic caspase control of mtDNA signaling (129-132). Additional AD-focused models link NLRP3 to A β and tau pathology and support a causal contribution of cGAS/STING signaling in 5xFAD and amyloid β -related disease (133-136). Table I summarizes key modular metrics and readouts for stratifying this circuit, enabling rapid staging and more appropriate target selection across models and sample types.

Why stratification matters: Circuit strength defines dominant edges and therapeutic windows. In NDDs, mitochondrial stress-induced mtDNA leakage can activate cGAS/STING and drive inflammatory transcription programs and inflammasome amplification, forming a supply-response-amplification reinforcement process. However, available evidence also indicates that this circuit does not operate identically across models, cell types or disease stages: In some contexts, DNA sensing and transcriptional responses dominate, whereas in others, the system has progressed to an amplification phase driven by inflammasomes and pyroptosis, with clear differences in intensity and dominant nodes (24,80,119,120,122). Treating all individuals or stages as the same inflammatory state and applying a uniform anti-inflammatory strategy can therefore lead to unstable efficacy and, in certain contexts, increased infection risk or impaired immune surveillance.

Modular readouts for circuit stratification. To obtain comparable conclusions across models, tissues and biofluids, circuit-stratification metrics may be organized into three modules that can be assessed independently and interpreted jointly: The input layer (mtDNA/ox-mtDNA supply), the chronicity layer (cGAS/STING output) and the amplification layer (NLRP3-pyroptotic execution).

Input layer: mtDNA/ox-mtDNA supply. Preferably quantify cell-free mtDNA (cf-mtDNA) levels and structural features, and ox-mtDNA/oxidized-DNA markers in plasma or cerebrospinal fluid (adding EV fractions when needed) to assess whether leakage supply is sustained, and interpret these alongside biofluid mtDNA abnormalities reported in disease cohorts (18,137-139).

Chronicity layer: cGAS/STING output (IFN-I and NF- κ B). Use an ISG signature to represent IFN-I axis strength, together with phosphorylated (p-)STING/p-TBK1/p-IRF3 and NF- κ B-related indicators, to distinguish ‘IFN-dominant’ from ‘inflammatory-transcription-biased’ STING outputs (31,120,122).

Amplification layer: NLRP3-pyroptosis module. Combine mature IL-1 β /IL-18 (products) with caspase-1 activation, GSDMD-N cleavage and ASC specks (execution/structural markers) to determine whether the system has entered an amplification stage (140,141). Joint stratification across these three modules can rapidly localize the dominant segment across the supply-transcription-amplification layers, providing reproducible and comparable anchors for subsequent target selection and efficacy follow-up.

Table I. Module-wise readouts for stratifying the mtDNA-cGAS/STING-NLRP3 circuit.

Stage/module	Representative nodes/markers	Preferred sample & assay	How it stratifies the circuit	(Refs.)
STING branch selection	STING-TBK1 recruitment; p-TBK1, p-IRF3, p-p65; IFNB1 vs. TNFA/IL6 output	WB; qPCR; cytokine ELISA	Quantifies how one STING platform sets gain for IRF3 and NF-κB in parallel	(120)
STING non-IFN bias	TBK1 and IKKε redundancy for STING→NF-κB	Genetic/chemical inhibition + NF-κB readouts	Separates IFN-dominant vs. NF-κB-dominant STING outputs	(119)
STING ubiquitin organization	HOIP/LUBAC-driven linear (M1) ubiquitin chains on STING; NF-κB assembly	IP-WB for M1-Ub; pathway readouts	Explains IFN and NF-κB axis decoupling via platform-specific scaffolding	(122)
Tau→cGAS/STING priming	Tau-PQBP1-cGAS/STING axis in microglia; inflammatory programs	Microglia genetics; cytokines; transcriptomics	Defines tau-driven DNA-sensing priming that can elevate NLRP3-ready transcription	(126)
Tau fibrils→cGAS-IFN	Tau fibrils activate microglial cGAS-IFN signaling; ISGs	RNA-seq; Cgas ^{-/-} microglia comparisons	Stratifies tauopathy into IFN-high vs. IFN-low inflammatory phenotypes	(78)
Tau propagation & NF-κB state	Microglial NF-κB drives tau spreading and toxicity	Microglial state mapping; tau seeding assays	Links inflammatory transcription (NF-κB) to structural disease events (tau transmission)	(127)
α-Syn→DNA damage→cGAS/STING	Misfolded α-syn induces DNA damage and triggers cGAS/STING neuroinflammation	γH2AX; cGAS/STING readouts; microglial assays	Positions DNA damage-STING as an upstream inflammatory driver in synucleinopathy	(76)
STING in nigrostriatal α-synucleinopathy	STING mediates neurodegeneration and neuroinflammation in α-syn models	Sting ^{-/-} ; behavior; neuropathology	Supports STING as a stratification axis for PD-like inflammatory circuits	(128)
Aging/inflammaging (brain included)	cGAS-STING drives ageing-related inflammation and neurodegeneration	Aged tissues; STING blockade/KO; brain readouts	Defines ‘STING-high inflammaging’ subgroup prone to inflammasome amplification	(24)
Aging BBB coupling	Microglial STING safeguards against BBB breakdown with age	Aged mouse vascular leakage; micro-hemorrhage; microglia phenotypes	Stratifies phenotypes where STING impacts vascular-immune coupling, not only IFN output	(80)
ox-mtDNA exit routes	FEN1-cleaved ox-mtDNA fragments exit via mPTP/VDAC to activate STING and NLRP3	Cytosolic oxDNA; channel inhibition; IL-1β/IFN readouts	Operationalizes ‘ox-mtDNA availability’ as a shared input into STING and NLRP3	(18)
Cristae gatekeeping	Cristae architecture restrains mtDNA release; STING-dependent IFN readouts	EM; mitochondrial structure perturbation; cytosolic mtDNA assays	Defines a structural mitochondrial checkpoint for circuit entry	(129)
Nucleotide stress → mtDNA leakage	YME1L deficiency causes mtDNA release and cGAS-STING-TBK1 inflammation	Metabolomics; mtDNA leakage; ISG panel	Connects metabolic state to mtDNA leak propensity and downstream DNA-sensing gain	(31)
Parkin-VDAC1 checkpoint	Parkin ubiquitinates VDAC1 to restrict oligomerization and mtDNA release	VDAC1 oligomer assays; cytosolic mtDNA; STING activation	Mechanistic node linking mitophagy/ubiquitin control to mtDNA escape threshold	(130)

Table I. Continued.

Stage/module	Representative nodes/markers	Preferred sample & assay	How it stratifies the circuit	(Refs.)
Endosomal mitophagy restrains NLRP3	APPL1-Rab5 axis promotes mitophagy and limits NLRP3 hyperactivation	Mitophagy flux; IL-1 β /caspase-1 readouts	Defines a ‘clearance capacity’ axis modulating amplification and secondary mtDNA stress	(125)
NLRP3→mitophagy suppression (disease model)	NLRP3 activation inhibits mitophagy in temporal lobe epilepsy model	Animal model; mitophagy markers; inflammasome activation	Supports bidirectional loop where amplification reduces clearance and sustains stress	(125)
Executioner pore→mitochondrial damage	GSDMD-NT permeabilizes mitochondrial membranes early in pyroptosis; mtDNA release	Cleaved GSDMD; $\Delta\Psi_m$; cytosolic mtDNA	Links inflammasome execution to renewed mitochondrial stress and circuit re-entry	(140)
Fluid biomarker for inflammasome activity	ASC specks as single-molecule fluid biomarker	Blood/CSF; single-molecule detection assays	Practical PD/AD stratification readout for inflammasome activation intensity	(141)
CSF mtDNA deletions (prodromal LBD)	cf-mtDNA deletion burden in idiopathic REM sleep behavior disorder CSF	CSF long-range PCR/NGS; longitudinal follow-up	Defines ‘mtDNA-dysfunction-high’ prodromal subgroup linked to LBD conversion risk	(139)
Salivary mtDNA (non-invasive AD association)	Salivary mtDNA copy number correlates with cortical A β and plasma pTau181	Saliva qPCR/ddPCR + PET/ biomarker correlations	Low-burden screening for systemic mtDNA-high signature linked to AD pathology	(138)
ALS trigger (proteinopathy→mtDNA leak)	TDP-43 triggers mtDNA release via mPTP to activate cGAS/STING	ALS models; mtDNA leakage assays; STING readouts	Defines proteinopathy-driven entry into the mtDNA-STING arm of the circuit	(137)
Sensing efficiency amplifier	Cytosolic TOP3 α facilitates mtDNA sensing by cGAS	Cell-free reconstitution; cGAS-mtDNA binding; mutational analysis	Stratifies individuals by ‘sensing gain’ independent of mtDNA supply	(131)
mtDNA release (live-cell OMM pore)	VDAC oligomerization; cytosolic mtDNA fragments; IFN-I/ISGs	OMM pore assays; cytosolic mtDNA qPCR/ddPCR; ISG qPCR	Defines ‘mtDNA supply-high’ state driven by OMM pores in stressed but viable cells	(16)
Apoptosis gate (immune silence)	Caspase activation; Bax/Bak-MOMP; cGAS/STING-IFN β suppression	Caspase activity; MOMP readouts; IFNB1/ISGs	Separates silent apoptosis vs. DNA-sensing-active death phenotypes	(132)
Apoptosis gate (genetic support)	Caspase blockade/KO unmasks mtDNA→cGAS/STING→IFN-I	Genetic models + IFN/ISG panels	Confirms caspases as a key switch controlling mtDNA immunogenicity	(35)
mtDNA stress → cGAS/STING entry	mtDNA instability/stress; cGAS-STING-IRF3 activation	mtDNA stress models; cytosolic mtDNA; p-IRF3/ISGs	Marks DNA-sensing primed background before overt inflammasome amplification	(13)
Large pore/herniation route (apoptosis)	BAK/BAX macropores; mitochondrial herniation; mtDNA efflux	Live-cell imaging; mtDNA efflux assays	Identifies structural route for high-intensity mtDNA release during MOMP	(34)

Table I. Continued.

Stage/module	Representative nodes/markers	Preferred sample & assay	How it stratifies the circuit	(Refs.)
ox-mtDNA → NLRP3 activation	Oxidized mtDNA; NLRP3-caspase-1; IL-1β/IL-18	ox-mtDNA detection; caspase-1 activity; IL-1β ELISA	Connects mitochondrial oxidative stress to the NLRP3 amplification edge	(20)
NLRP3 in AD (Aβ pathology)	Active caspase-1; NLRP3 activation; microglial inflammation	Brain tissue; inflammasome readouts; pathology/behavior	Stratifies AD-like states with inflammasome-high contribution to pathology	(133)
ASC specks as Aβ amplifier	Extracellular ASC specks; Aβ seeding/cross-seeding	ASC speck assays; seeding assays; pathology spread	Adds a propagation layer for inflammasome output beyond cytokines	(8)
NLRP3 ↔ tau axis	tau-induced NLRP3; NLRP3 loss reduces tau pathology	Tau pathology assays; inflammasome readouts	Captures tauopathy-dominant NLRP3-to-structural pathology edge	(134)
cGAS/STING in AD (5xHAD)	Microglial cGAS/STING activation; neuroinflammation; Aβ pathology	Mouse brain; cGAS/STING markers; pathology/behavior	Defines STING-high AD subgroup (DNA-sensing-driven neuroinflammation)	(135)
Genetic causality (STING deletion)	STING KO reduces Aβ-driven pathology	KO + pathology/behavior panels	Separates STING-causal vs. STING-bystander inflammatory signatures	(136)
Therapeutic stratifier (STING blockade)	STING inhibition improves microglial dysfunction and AD endpoints	Inhibitor studies; microglial state + pathology	Provides actionable readouts for STING-dependent vs. independent pathology	(74)
Genetics x microglial cGAS program	AD risk alleles elevate microglial cGAS-linked senescence	Microglial senescence markers; cGAS/IFN modules	Stratifies cGAS-senescence-high tauopathy progression phenotype	(75)
Fluid biomarker (inflammasome output)	extracellular ASC specks in serum/CSF; morphology/abundance	Single-molecule pull-down/imaging assays	Quantifies inflammasome output intensity for patient stratification	(141)

5xHAD, five familial Alzheimer's disease mutations; Aβ, amyloid β; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APPL1, adaptor protein containing a pleckstrin homology domain, a phosphotyrosine-binding domain and a leucine zipper motif 1; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; α-syn, α-synuclein; BAK, B-cell lymphoma 2 antagonist/killer 1; BAX, B-cell lymphoma 2-associated X protein; BBB, blood-brain barrier; cf-mtDNA, cell-free mitochondrial DNA; cGAS, cyclic GMP-AMP synthase; Cgas^{-/-}, cGAS-knockout genotype; CSF, cerebrospinal fluid; ddPCR, droplet digital polymerase chain reaction; DNA, deoxyribonucleic acid; ELISA, enzyme-linked immunosorbent assay; EM, electron microscopy; FEN1, flap structure-specific endonuclease 1; γH2AX, histone H2AX phosphorylated at serine 139; GSDMD, gasdermin D; GSDMD-NT, N-terminal fragment of gasdermin D; HOIP, HOIL-1-interacting protein; IFN-I, type I interferon; IFNB1, interferon β1; IKKε, inhibitor of nuclear factor κB kinase subunit ε; IL-1β, interleukin 1β; IP-WB, immunoprecipitation followed by western blotting; IRF3, interferon regulatory factor 3; ISG(s), interferon-stimulated gene(s); KO, knockout; LBD, Lewy body disease; LUBAC, linear ubiquitin chain assembly complex; M1, methionine 1 linkage; M1-Ub, methionine 1-linked ubiquitin; MOMP, mitochondrial outer membrane permeabilization; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; NF-κB, nuclear factor κB; NGS, next-generation sequencing; NLRP3, NLR family pyrin domain containing 3; OMM, outer mitochondrial membrane; oxDNA, oxidized DNA; ox-mtDNA, oxidized mitochondrial DNA; PCR, polymerase chain reaction; PD, Parkinson's disease; PET, positron emission tomography; p-IRF3, phosphorylated IRF3; p-p65, phosphorylated NF-κB p65 subunit; p-TBK1, phosphorylated TBK1; pTau181, tau phosphorylated at threonine 181; PQBP1, polyglutamine-binding protein 1; qPCR, quantitative polymerase chain reaction; Rab5, Ras-related protein Rab-5; Refs., references; REM, rapid eye movement; RNA-seq, RNA sequencing; STING, stimulator of interferon genes; Sting^{-/-}, STING-knockout genotype; TBK1, TANK-binding kinase 1; TDP-43, TAR DNA-binding protein 43; TNF, tumor necrosis factor; TOP3α, DNA topoisomerase IIIα; VDAC, voltage-dependent anion channel; VDAC1, voltage-dependent anion channel 1; WB, western blotting; YME1L, YME1-like protein 1 ATPase; ΔΨm, mitochondrial membrane potential; →, directional relationship; ↔, bidirectional relationship.

Mapping stratification to interventions. Here, a module-based decision logic is proposed, which, within a unified circuit framework, translates observed stratification readouts into prioritized intervention directions and specifies the validation metrics that should be followed in parallel.

If cf-mtDNA or ox-mtDNA remains persistently elevated, prioritize source-control strategies-reducing mtDNA escape and enhancing MQC and lysosomal disposal. Antioxidant or metabolic support can be used to reduce ox-mtDNA generation, and follow-up should track decreases in biofluid

mtDNA together with downstream ISG and IL-1 axis readouts (18,20,31,125,140). If NF- κ B-related readouts downstream of cGAS-STING are high but the ISG signature is not, treat this as an inflammatory-transcription-biased output. Interventions should not focus solely on the IFN axis, but instead consider STING platform organization and its bias toward NF- κ B; follow-up should emphasize normalization of NF- κ B-linked transcription rather than ISGs alone (119,120,122). If the ISG signature is clearly elevated (IFN-I dominant), this better fits a DNA-sensing-driven chronicity phenotype; strategies should focus on limiting sustained STING activation and upstream inputs, while monitoring anti-infective risk and immune-surveillance indicators to avoid vulnerability from prolonged strong suppression (31,120). If amplification-layer markers are high (elevated mature IL-1 β /IL-18, ASC specks or GSDMD-N positivity), prioritize terminal ‘load reduction’ to break self-amplification, while simultaneously assessing whether the input layer remains high; if upstream supply does not fall, terminal suppression alone is often not durable and rebound is more likely after withdrawal or dose reduction (13,16,18,125,140,141).

If all three modules are highly active (Loop-High), a stratified combination approach is more appropriate: First reduce terminal burden to rapidly limit tissue injury, then add source control and output correction to stabilize the system. Follow-up should cover biofluid mtDNA, ISG modules and inflammasome-execution markers to form a verifiable closed loop (13,16,18,20,120,140).

Combination therapy, delivery and safety. Single-point inhibition is often insufficient because lowering terminal inflammation is not equivalent to suppressing the upstream circuit. Inhibiting the IL-1 axis or pyroptotic execution can transiently reduce tissue injury, but if mtDNA leakage and upstream transcriptional drive are not concurrently reduced, signal rebound and flare risk increase after withdrawal or dose reduction (121-123). Conversely, without stratification, prolonged broad inhibition of DNA sensing or IFN-related pathways may weaken anti-infective defense and tumor immune surveillance; STING-dependent DNA sensing is considered to participate in tumor recognition and anti-tumor immune responses (124,125). Within the CNS, the biological meaning of the same target differs across cell populations: Microglial state transitions and functional programs- and their interactions with astrocytes-reshape inflammatory output and tissue effects, making cell-type differences a key determinant of efficacy and safety (137). Therefore, combination therapy should be coupled with delivery strategies, prioritizing systems that cross the BBB and enhance cellular selectivity (138) to reduce systemic immune costs and widen the therapeutic window.

Recommendations for clinical trials and animal study design. At study initiation, define Loop-High and Loop-Low states using the three-module composite indicators specified above, and stratify baseline cohorts accordingly to control mechanistic heterogeneity. During follow-up and treatment, use the same composite indicators as pharmacodynamic readouts to validate coherent changes across decreased input supply, reduced STING output and weakened amplification

markers-thus forming a testable closed loop. If amplification markers decrease but the input layer does not, upstream supply likely continues to drive the circuit and durability may be limited; consider adding source-control strategies or optimizing treatment windows to improve stability.

7. Discussion

Although disease-modifying therapies for NDDs have continued to emerge in recent years-particularly in AD, where anti-A β monoclonal antibodies have shown some degree of clinical slowing in randomized controlled trials-overall benefits remain modest and are accompanied by issues of safety and accessibility (142-144). As a result, whether these approaches stably modify disease course and the magnitude of their clinical relevance remain under active debate, including controversies over endpoint interpretation, eligible populations, the risk of amyloid-related imaging abnormalities and long-term outcomes (142-144). Meanwhile, population aging continues to drive the neurological disease burden upward, amplifying the demand for scalable and reproducible therapeutic strategies (145). More importantly, immune and metabolic contexts differ across NDDs- and even across stages within the same disease. Single-cell studies and reviews increasingly emphasize that microglial states and their interactions with other glia and peripheral myeloid cells are highly context dependent, making a uniform anti-inflammatory pathway unlikely to deliver consistent effects in all patients (146). Against this background, rather than focusing on a single pathway or a single pathological protein, this review frames discussion around a coupled circuit in which mtDNA escape provides an upstream input and cGAS/STING transcriptional output and NLRP3 amplification/execution serve as key nodes. This framework may help explain neuroinflammatory heterogeneity and provide more testable logic for classification experiments and target matching.

Increasingly, chronic inflammation in NDDs is viewed as the outcome of long-term coupling between mitochondrial stress and innate immunity, with mtDNA escape providing a testable upstream input (147,148). Mechanistically, ALS-associated pathology involving TAR DNA-binding protein 43 (TDP-43) can promote mtDNA entry into the cytosol through mPTP and activate cGAS/STING, suggesting that mitochondrial membrane events can ‘transcribe’ endogenous neuronal stress into persistent immune signaling (137). It is also important that oxidized DNA fragments can escape via mPTP- and VDAC-associated routes and, within the same cellular background, simultaneously trigger INF signaling and NLRP3 inflammasome responses-supporting parallel initiation of cGAS/STING and NLRP3 (18). Such inputs do not only arise at late stages of cell death; metabolic stress can also induce mtDNA-linked innate immune responses, indicating that circuit strength is strongly modulated by cellular state and metabolic environment (31). In disease-relevant models, causal links between microglial STING activation and neuroinflammation/neuron injury have been supported in α -syn-related PD-like pathology, and aging-associated cGAS-STING activity can drive reactive microglial transcriptional states with neurodegenerative phenotypes (24). Notably, neither upstream sources nor downstream outputs of

cGAS/STING are fixed: The DNA source can shift between mtDNA and nuclear DNA damage across models, and STING can bias toward NF- κ B rather than IFN-I under certain conditions, in a manner related to signal-assembly organization (24,122,149,150). Thus, instead of simplifying NDDs as a single ‘inflammation increase’, it is more informative to view mtDNA-cGAS/STING-NLRP3 as a circuit whose strength is jointly determined by input supply, transcriptional output and amplification execution- and to apply a classification logic to interpret differences and match interventions.

Importantly, the mtDNA-cGAS/STING-NLRP3 axis is not rigid but resembles a reconfigurable signaling assembly. In some contexts, micronuclei generated by nuclear DNA damage can become the primary source of cytosolic DNA and drive cGAS activation, shifting the upstream DNA source between mtDNA and nuclear DNA (151). In addition, STING downstream outputs show spatial and temporal differences. Recent work indicates that after leaving the Golgi apparatus, STING can signal at late endosome/lysosome-associated sites, recruiting TRAF6 via an IRF3 adaptor and thereby biasing toward NF- κ B output without strict synchrony with IFN-I (152). Meanwhile, spatiotemporal control of the STING platform by linear ubiquitin chains can further shape the signaling-assembly environment, helping explain the decoupling between IFN and NF- κ B programs across models (153). When the circuit enters the amplification layer, pyroptotic pores and mitochondrial membrane events can in turn increase mtDNA exposure and co-engage cGAS/STING and NLRP3. Recent studies link gasdermin-associated mtDNA release to co-activation of both axes, suggesting that terminal load reduction without source control makes reactivation more likely (154,155). Thus, whether the mitophagy-lysosome axis can promptly remove damaged mitochondria often determines whether the circuit is interrupted. Inducing mitophagy has been shown to reduce cytosolic mtDNA and suppress cGAS/STING-driven chronic inflammatory phenotypes. In NDD contexts, Parkin-mediated limitation of microglial NLRP3 also supports a braking role of MQC on the amplification layer (156). Notably, although a classic piece of evidence for PINK1/Parkin restraining sterile inflammation via direct STING suppression was later retracted, this does not negate the core logic of mtDNA-driven inflammation; rather, it emphasizes that autophagy acts primarily by source control rather than direct inhibition of signaling proteins (157). Consistently, STING deficiency in *Drosophila* alleviates parkin mutation-associated muscle and mitochondrial dysfunction (158). Together, these results suggest species- and tissue-specific feedback structures between MQC defects and STING signaling, and highlight the need to distinguish cell types and disease stages in translational studies. Overall, mtDNA-cGAS/STING-NLRP3 is best viewed as a reconfigurable circuit shaped by DNA source, STING output bias and MQC; therefore, dominant-edge differences across models and stages make classification-based assessment and combination interventions more reliable than single-node inhibition.

To translate the mtDNA-cGAS/STING-NLRP3 axis into effective therapeutic strategies, the key is to establish an integrated evaluation system that captures the three functional modules, rather than relying solely on inflammatory cytokines (141,159). Such multidimensional assessment not only

defines the operating mode of the circuit but also enables a pharmacology-to-clinic closed loop. Therapeutically, this implies moving from generic anti-inflammation toward precise blockade of upstream sources and load reduction at effector ends. Given the infection risks potentially associated with long-term suppression of terminal anti-inflammatory/inflammasome/pyroptosis pathways (160), CNS-targeted delivery technologies will be crucial for enlarging the immune safety window while reducing systemic immune costs. NLRP3 also mediates peripheral organ injury. In hepatic ischemia/reperfusion models, the SET domain-containing protein 8/microtubule affinity-regulating kinase 4 pathway (161), liver kinase B1 (162), the glycogen synthase kinase 3 β /AMPK pathway (163) and cytidine/uridine monophosphate kinase 2 (164) regulate NLRP3 activation and liver damage, suggesting that CNS NLRP3 modulation may influence peripheral organs through systemic inflammatory communication, although direct evidence remains limited. Future work should test whether synergistically combining reductions in mtDNA supply with inhibition of inflammasome execution yields more stable and reproducible neuroprotection than single interventions.

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Availability of data and materials

No new data were generated or analyzed in this review; therefore, data sharing is not applicable to this article.

Authors' contributions

HL, YZ and ZLZ contributed equally to this work as co-first authors. HL and YZ conceived the study, performed the literature search and data synthesis, drafted the initial manuscript and designed the figures and tables. ZZ participated in the literature screening, data extraction and interpretation of immunological mechanisms. WZ and MY assisted in the analysis of the cGAS/STING-NLRP3 signaling cascade and the therapeutic implications in neurodegenerative diseases. ZBZ supervised the project, acquired funding, provided critical revision of the manuscript for important intellectual content and finalized the version to be published. Data authentication is not applicable. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, ChatGPT and the GPT-5.6 Sol model (OpenAI) was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript

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