Molecular Neurodegeneration

REVIEW

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The neuroimmune nexus: unraveling the role of the mtDNA-cGAS-STING signal pathway in Alzheimer's disease

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Abstract

The relationship between Alzheimer's disease (AD) and neuroimmunity has gradually begun to be unveiled. Emerging evidence indicates that cyclic GMP-AMP synthase (cGAS) acts as a cytosolic DNA sensor, recognizing cytosolic damage-associated molecular patterns (DAMPs), and inducing the innate immune response by activating stimulator of interferon genes (STING). Dysregulation of this pathway culminates in AD-related neuroinflammation and neurodegeneration. A substantial body of evidence indicates that mitochondria are involved in the critical pathogenic mechanisms of AD, whose damage leads to the release of mitochondrial DNA (mtDNA) into the extramitochondrial space. This leaked mtDNA serves as a DAMP, activating various pattern recognition receptors and immune defense networks in the brain, including the cGAS-STING pathway, ultimately leading to an imbalance in immune homeostasis. Therefore, modulation of the mtDNA-cGAS-STING pathway to restore neuroimmune homeostasis may offer promising prospects for improving AD treatment outcomes. In this review, we focus on the mechanisms of mtDNA release during stress and the activation of the cGAS-STING pathway. Additionally, we delve into the research progress on this pathway in AD, and further discuss the primary directions and potential hurdles in developing targeted therapeutic drugs, to gain a deeper understanding of the pathogenesis of AD and provide new approaches for its therapy.

Keywords MtDNA, cGAS, STING, Neuroinflammation, Alzheimer's disease, Treatment

Background

Alzheimer's disease (AD) is the most common form of chronic neurodegenerative disease, posing significant health risks to the elderly [1]. Clinically, it primarily manifests as a progressive impairment of memory and cognitive function [2]. Analysis of epidemiological data has indicated that the global prevalence of dementia is expected to triple by 2050, imposing heavy economic and psychological challenges on communities and households [3–5]. The primary pathological features of AD involve the widespread amyloid plaques and neurofibrillary tangles (NFT) within the brain, triggering irreversible neuronal damage and cognitive decline [6]. Despite significant global financial investments for tackling AD, effective treatment strategies are still lacking [7]. One possible reason for this is that the etiology of AD is multifactorial [8], and the precise molecular mechanisms underlying its onset and progression remain largely elusive. As such, there is an urgent need to explore new disease-modifying therapies that target the critical processes of AD pathogenesis [9], with the aim of obtaining better treatment outcomes. Recent studies have identified the involvement of maladaptive inflammatory responses and immune dysregulation in AD development [10, 11], highlighting the importance of understanding the potential

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molecular mechanisms underlying immune-inflammatory reactions.

The innate immune, serving as the first line of defense in the body's immune system, can distinguish between "self" and "non-self" effectively [12]. Endogenous damage-associated molecular patterns (DAMPs) released after cellular damage, such as self-proteins or nucleic acids, can also be recognized by the innate immune system, thereby eliciting a swift and non-specific immune response [13]. This recognition process is mediated by pattern recognition receptors (PRRs), the majority of which possess sequence- and cell-type- specificity [14]. Notably, as a unique type of PRRs, cyclic GMP-AMP synthase (cGAS) lacks DNA sequence specificity, and cannot effectively distinguish between self and foreign DNA [15]. Consequently, mitochondrial DNA (mtDNA) and other double-stranded DNA (dsDNA) can act as DAMPs to bind cGAS upon entry into the cytoplasm, thus activating the downstream stimulator of interferon genes (STING) [16]. Typically, the cGAS-STING pathway serves as a protective mechanism against invading pathogens, and its activation by external nucleic acids, such as those from viruses, can effectively protect the cells from potential threats [17]. However, overactivation of this pathway, triggered by the accumulation of ectopic dsDNA in the central nervous system (CNS), may exacerbate neuroinflammatory responses. This dysregulated inflammatory environment likely further impairs neuronal cells, causing damage to healthy tissues and potentially triggering multiple neurological diseases that have been reported to be associated with abnormal inflammation, including AD, Parkinson's disease (PD) [18], amyotrophic lateral sclerosis (ALS) [19], postoperative cognitive dysfunction (POCD) [20], and traumatic brain encephalopathy (TBE) [21], although the pathogenesis of these diseases shows high heterogeneity. Recent studies particularly highlight its critical role in AD.

In this review, we summarize how mtDNA is released into extramitochondrial space under cellular stress, and subsequently recognized by the cGAS-STING signal pathway. Furthermore, we discuss the pivotal role of the mtDNA-cGAS-STING pathway in AD and the prospects of targeting this pathway for AD treatment. We believe that an in-depth exploration of the mechanisms related to this cascade pathway will provide greater hope for delaying AD progression.

Mechanisms of mtDNA release

In mammalian cells, mtDNA is a double-stranded, circular DNA comprising 16,569 base pairs and encoding 37 genes [22]. mtDNA is distributed throughout the mitochondrial network, and the proteins it encodes are involved in a wide range of physiological functions [23], including energy supply, Ca^{2+} homeostasis maintenance, synaptic plasticity [24], and heme and cholesterol synthesis [25]. Notably, mtDNA itself exerts an endogenous pro-inflammatory effect, which is largely attributed to its unmethylated CpG islands, akin to bacterial genomes [26, 27]. As such, mtDNA released outside of mitochondria can act as an immune stimulant to mediate immune-inflammatory processes. Nevertheless, mtDNA possesses an intricate set of self-protection systems that protect it from recognition by the immune surveillance system under physiological conditions, thus maintaining its relatively stable existence within cells. These mechanisms encompass the barrier of the mitochondrial "double-layer" membrane, balanced mitochondrial dynamics, coordinated regulation of various nuclear genes, mitochondrial autophagy, and interplay with other cellular organelles [28–30]. Abnormalities in these mechanisms may lead to mtDNA mutations or relocation outside the mitochondria, although the specific release process and related regulatory mechanisms remain unclear. Interestingly, the mechanisms underlying mtDNA releasing to extramitochondrial space differ between apoptotic and living cells; in cells under apoptotic stress, mtDNA escape predominantly occurs through macropores formed by apoptotic regulators (BAK/BAX) [31, 32], including in senescent cells that remain resistant to apoptosis, where mtDNA can also be released via BAK/BAX-dependent minority MOMP (miMOMP) [33]. Whereas in living cells, mtDNA primarily depends on voltage-dependent anion channel (VDAC) oligomerization pores in the outer mitochondrial membrane (OMM) that promote mitochondrial outer membrane permeabilization (MOMP) [34, 35]. Besides, gasdermin pores, mitochondrial dynamics, extracellular vesicles (EVs), and neutrophil extracellular traps (NETs) also contribute to mtDNA release [36]. As such, mtDNA escape is an exceedingly complex process involving an interplay of multiple mechanisms. In the following sections, we systematically summarize these mechanisms of mtDNA release to better understand the role of mtDNA in inflammatory diseases and immune regulation.

The mechanism of mtDNA release into the extramitochondrial space

BAK/BAX pores

The prevailing view supports the notion that MOMP is the primary trigger of mtDNA release. When apoptotic signals occur within cells, the pro-apoptotic factors BAX and BAK are activated and recruited to oligomerize on the OMM, forming macropores that induce MOMP [37]. The growth rate of these macropores and the relative kinetics of mtDNA are influenced by the relative availability of Bax and Bak, while their interactions can

regulate the dynamics of mtDNA release [38, 39]. Unlike non-inflammatory mitochondrial apoptosis, which relies on caspase activation, mtDNA release through these macropores does not require activated caspases [32]. The absence of the latter is crucial for mtDNA-mediated inflammation. If caspases are activated, cell death occurs after MOMP, without triggering the type I interferon (IFN) response [40, 41]. In other words, caspase activation can sequester the apoptotic process of cells from the immune system, thus avoiding unnecessary inflammatory responses. This precise regulatory mechanism ensures the orderly progression of apoptosis, which is important for maintaining immune homeostasis in organisms.

Following MOMP, the inner mitochondrial membrane (IMM) protrudes into the cytoplasm through BAK/BAX macropores to form mitochondrial herniations. Then, the mitochondrial matrix contents, including the mitochondrial genome and other mitochondrial components, are translocated outside the mitochondria [31], subsequently activating caspase-independent cell death (CICD)-associated inflammation. This process may further result in a loss of IMM integrity, culminating in mitochondrial inner membrane permeabilization (MIMP) [32]. Additionally, studies have indicated that mtDNA is released into the cytoplasm in the form of entire nucleoids. However, whether these released nucleoids remain intact or fragmented remains unclear [42]. Clarifying the fate and effects of these released nucleoids within the cytoplasm is crucial, as they may be closely linked to the potential of mtDNA as an effective biomarker.

Notably, MOMP may also be associated with the release of mitochondrial double-stranded RNA (mt-dsRNA) [43]. Dhir et al. found that the release of mt-dsRNA is almost entirely blocked by the downregulation of BAX and BAK, indicating that mt-dsRNA release may predominantly occur via MOMP. These released mt-dsRNAs can also be recognized by dsRNA sensors and activate the IFN-I pathway [44]. Furthermore, they may act as mitochondrial self-antigens involved in the development of autoimmune diseases [45]. Nevertheless, the mechanisms underlying mt-dsRNA release remain poorly understood, and their precise role in immune responses requires further investigation.

VDAC oligomer pores

In living cells, the mechanism by which mtDNA is released is not uniform. Multiple studies have indicated that oxidative stress, when insufficient to activate BAK and BAX, can induce VDAC oligomerization and subsequently form pores in the OMM, thus promoting MOMP in living cells and facilitating mtDNA release [34]. Notably, mtDNA translocation through VDAC requires the coordination of other proteins, particularly the adenine nucleotide translocator (ANT) located in the IMM, and Cyprin D in the matrix. These proteins are considered key components of the mitochondrial permeability transition pore (mPTP), a diverse protein complex located between the IMM and OMM [46, 47]. García et al. provided evidence to support this view, showing that cyclosporin A, a Cyprin D inhibitor, could affect the permeability transition pore and inhibit mtDNA release into the cytoplasm by 52% [48]. Unlike the BAK/BAX pores, mtDNA fragments, which are components of specific genes, are released via VDAC pores [49]. In addition, mPTP pores are expected to allow only mtDNA fragments with a molecular weight of less than 1.5 kDa to pass through [50], enriching evidence that the mtDNA released via VDAC pores are fragments rather than intact nucleoids.

The formation of VDAC oligomer pores is a complex process regulated by several factors. Upon entry into the mitochondrial intermembrane space, mtDNA fragments themselves interact with residues at the N-terminus of the VDAC1 subtype, thus promoting VDAC oligomerization and forming a feed-forward loop [34]. The virus-related kinase 2 (VRK2) protein, a member of the vaccinia virus-related kinase family and a serine/threonine kinase with catalytic activity [51, 52], is considered another important regulator of VDAC1 oligomerization during mtDNA release. VRK2 was recently shown to induce cGAS-mediated innate immune response [53], indicating its potential as a therapeutic target for infectious and autoimmune diseases associated with mtDNA release. Additionally, Baik et al. demonstrated that the dissociation of hexokinase 2 (HK2) from VDAC triggers calcium release from the endoplasmic reticulum (ER), which is subsequently taken up by the mitochondria, leading to VDAC oligomerization and mtDNA escape [54]. However, these studies only partly elucidated the regulatory mechanisms governing mtDNA release through VDAC oligomeric pores, and their findings are likely limited to specific disease contexts. Further research is therefore needed to investigate whether there are differences in the regulation of mtDNA release through VDAC oligomeric pores under various disease conditions such as infection, autoimmune diseases, and cancer, which will help to identify specific therapeutic targets to provide more possibilities for the treatment of these related diseases.

Gasdermin pores

Gasdermins (GSDMs) are a class of pore-forming proteins that represent another channel for mtDNA escape from mitochondria [55]. As a pivotal effector molecule in pyroptosis, gasdermin undergoes cleavage by activated caspases to generate an N-terminal domain, that inserts into the plasma membrane and oligomerizes to form large pores through its pore-forming activity [56],

allowing the release of inflammatory substances like interleukin-1β (IL-1β) [57]. Huang et al. indicated that mtDNA can be released into the cytosol through gasdermin pores to activate downstream signaling pathways during inflammatory injury [58]. In detail, several members of the gasdermins, including gasdermin A3, gasdermin D (GSDMD), and gasdermin E, can facilitate mtDNA release during apoptosis or pyroptosis, and inhibit the pore activity of GSDMD significantly impedes this process, consequently ameliorating mitochondrial network structure damage and rescuing mitochondrial dysfunction [55, 59]. Additionally, oxidized mtDNA can directly interact with the GSDMD-N domain to enhance its oligomerization during the pore-forming process [60], which may exacerbate mitochondrial membrane rupture. Furthermore, membrane damage induced by gasdermin could precipitate the collapse of the mitochondrial network system, potentially providing alternative pathways for mtDNA release, such as NETs [61], and ultimately resulting in the displacement of mtDNA outside the mitochondria or even extracellularly. These studies indicate a plausible interplay between gasdermin and damaged mitochondria, both promoting cell death. Overall, the formation of gasdermin pores is a significant determinant of mtDNA escape, extending its importance beyond pyroptosis.

The mechanism and significance of mtDNA release into the extracellular space

Diverse mtDNA forms have been detected in different biological fluids, such as plasma [62], serum [63], cerebrospinal fluid (CSF) [64], and synovial fluid [65], indicating the further release of mtDNA from the cytoplasmic compartment into the extracellular environment. Currently, the active release of mtDNA is believed to occur primarily through transportation via extracellular EVs or as components of NETs, whereas its passive release typically occurs during cell injury and death processes like apoptosis, necrosis, and pyroptosis [25]. Recent studies have suggested that the level of cell-free mtDNA (cf-mtDNA) released into the extracellular fluid is a significant biomarker that partly reflects the severity and prognosis of various inflammation-related diseases. For example, a correlation has been observed between higher mtDNA copy numbers (mtDNAcn) in circulation and better cognitive function [66]. Similarly, patients with coronary heart disease have lower mtDNA levels than the control group [67]. Interestingly, evidence suggests that only cf-mtDNA, and not mtDNA present in intact circulating mitochondria, can elicit an inflammatory response [68]. Understanding the mechanisms underlying mtDNA releasing into extracellular space and the pathophysiological functions of its various forms is essential to advance our knowledge of mitochondrial biology and its roles in health and disease.

Activation of cGAS-STING by Leaked mtDNA

As mentioned above, under physiological circumstances, mtDNA is encapsulated within the "double membrane" structure of mitochondria and does not disturb the immune system. Upon release into the cytoplasm or circulation, it acts as a potential immune stimulus, eliciting an inherent immune response in the body. Although the precise mechanisms by which mtDNA triggers inflammation have not yet been fully elucidated, it is widely recognized that mtDNA primarily affects immune responses through three important signaling pathways: the toll-like receptor-9 (TLR-9), cGAS-STING, and nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR), and pyrin domain-containing protein 3 (NLRP3) inflammasome pathways [69] (Fig. 1). Given that the association of TLR-9 and NLRP3 with mtDNA has been extensively summarized in many other excellent reviews [25, 70], herein, we primarily focused on the crosstalk between mtDNA and the emerging immune pathway cGAS-STING, which is increasingly being recognized for its role in AD.

Molecular mechanisms of the cGAS-STING pathway

Activation of the cGAS-STING pathway is an extremely complex process (Fig. 2). The molecular weight of cGAS is approximately 60 kDa, and it comprises an N-terminal region that mediates binding to cell membrane, a highly conserved nucleotidyltransferase core domain, and a male abnormal gene family 21 (Mab21) nucleotidyltransferase domain [71, 72]. The Mab21 domain is primarily involved in dsDNA binding, and structural defects in it cause cGAS to lose the ability to induce IFN-β expression [73]. Thus, maintaining structural integrity is especially important for the physical function of cGAS. Unlike other PRRs, cGAS binds to negatively charged dsDNA through electrostatic interactions and hydrogen bonds, which partly explains its lack of sequence-specific recognition [74, 75]. In other words, it can bind to various types of nucleic acids, such as dsDNA, RNA:DNA hybrids, ssDNA, and dsRNA, but the latter two lack the ability to rearrange the catalytic pocket of cGAS to activate it [76, 77]. In addition, the intracellular localization of cGAS remains controversial. Although most studies consider it a "cytoplasmic sensor" [78], recent research indicated that cGAS is present in the cell nucleus and membrane as well [79–82]. For example, the localization of cGAS is cell-cycle dependent [83, 84]; it is typically located in the cytoplasm of non-dividing cells but translocates into the nucleus during mitosis in proliferating cells, where it binds to chromatin DNA [85]. In

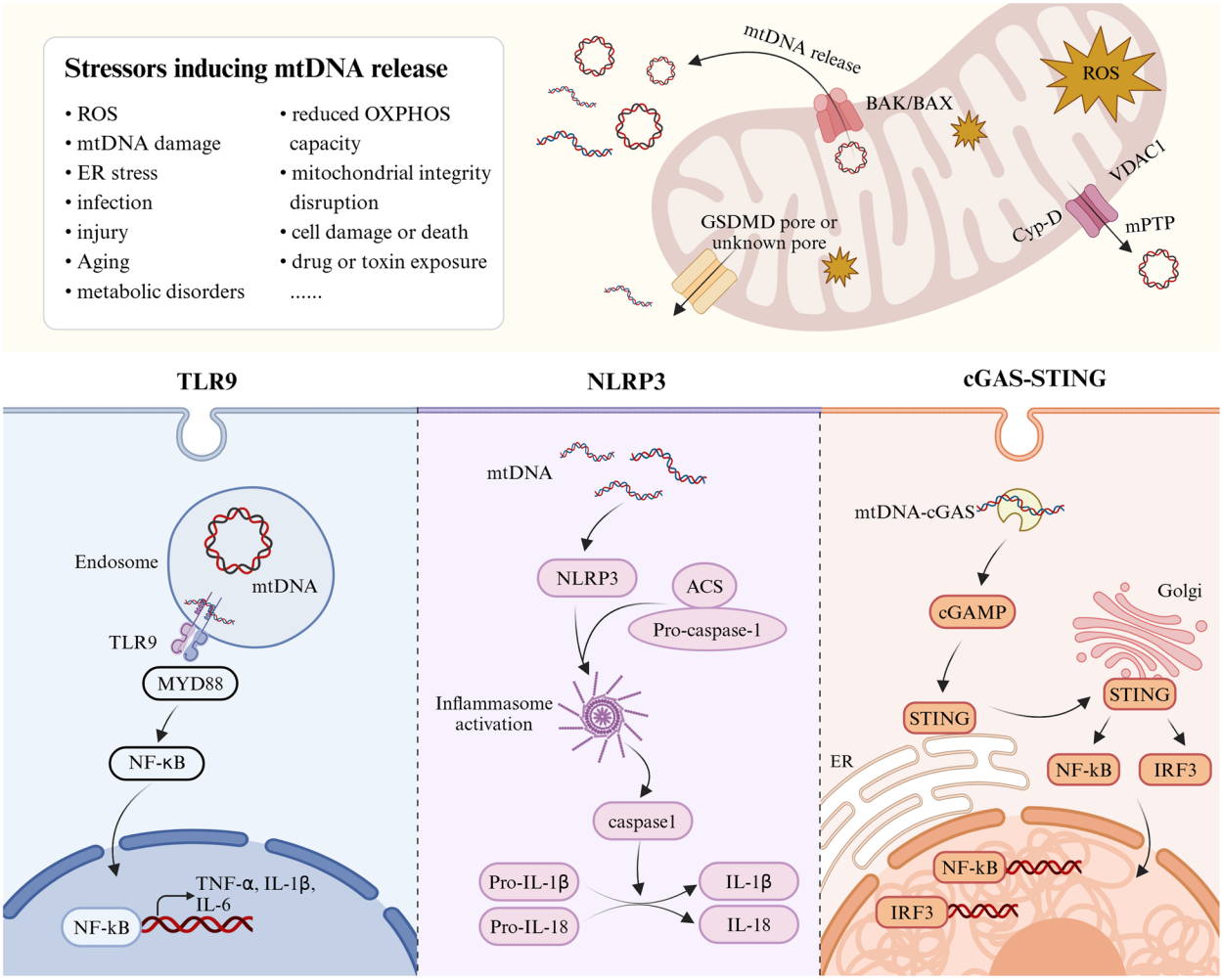

Fig. 1 Overview of the mechanisms of mtDNA release and its effect on the innate immune response. Under normal circumstances, mtDNA is encapsulated within mitochondria without disturbing the immune system. However, when exposed to various adverse factors such as ROS, cellular stress, and aging, mitochondria inevitably incur a certain degree of damage. At this point, mtDNA is released into the extramitochondrial space through mechanisms involving BAK/BAX, VDAC1, GSDMD, and others. Subsequently, the leaked mtDNA acts as DAMPs, recognized by diverse PRRs, primarily activating the body's innate immune response through three different inflammatory pathways: TLR9, NLPR3, and cGAS-STING

summary, its subcellular localization is tightly related to the cell types and biological contexts, allowing it to function more effectively.

Indeed, cGAS possesses catalytic inertness. When it binds to dsDNA, a conformational change occurs, converting the catalytic pocket of cGAS from an inactive "closed" conformation to an active "open" conformation, forming a 2:2 dimeric structure composed of cGAS and dsDNA [75, 86]. Subsequently, this complex catalyzes the formation of 2'3'-cyclic GMP-AMP (2'3'-cGAMP) from guanosine triphosphate (GTP) and adenosine triphosphate (ATP), which serves as a second messenger, binding and activating the adaptor protein STING located on the ER membrane, initiating a cascade of intracellular signaling events crucial for the immune response [87].

Ishikawa et al. first reported the importance of STING in the innate immune response to antiviral immunity. As an important component of nonspecific immunity against aberrant cytoplasmic DNA, STING is widely expressed in the ER across various cell types [88]. Upon binding to 2'3'-cGAMP, STING oligomerizes and is trafficked from the ER to the Golgi apparatus [89, 90]. During this process, the C-terminal tail (CCT) of STING recruits and activates TANK-binding kinase 1 (TBK1), which phosphorylates STING and interferon regulatory factor 3 (IRF3) [91]. Subsequently, phosphorylated IRF3 forms dimers and is translocated to the nucleus to bind

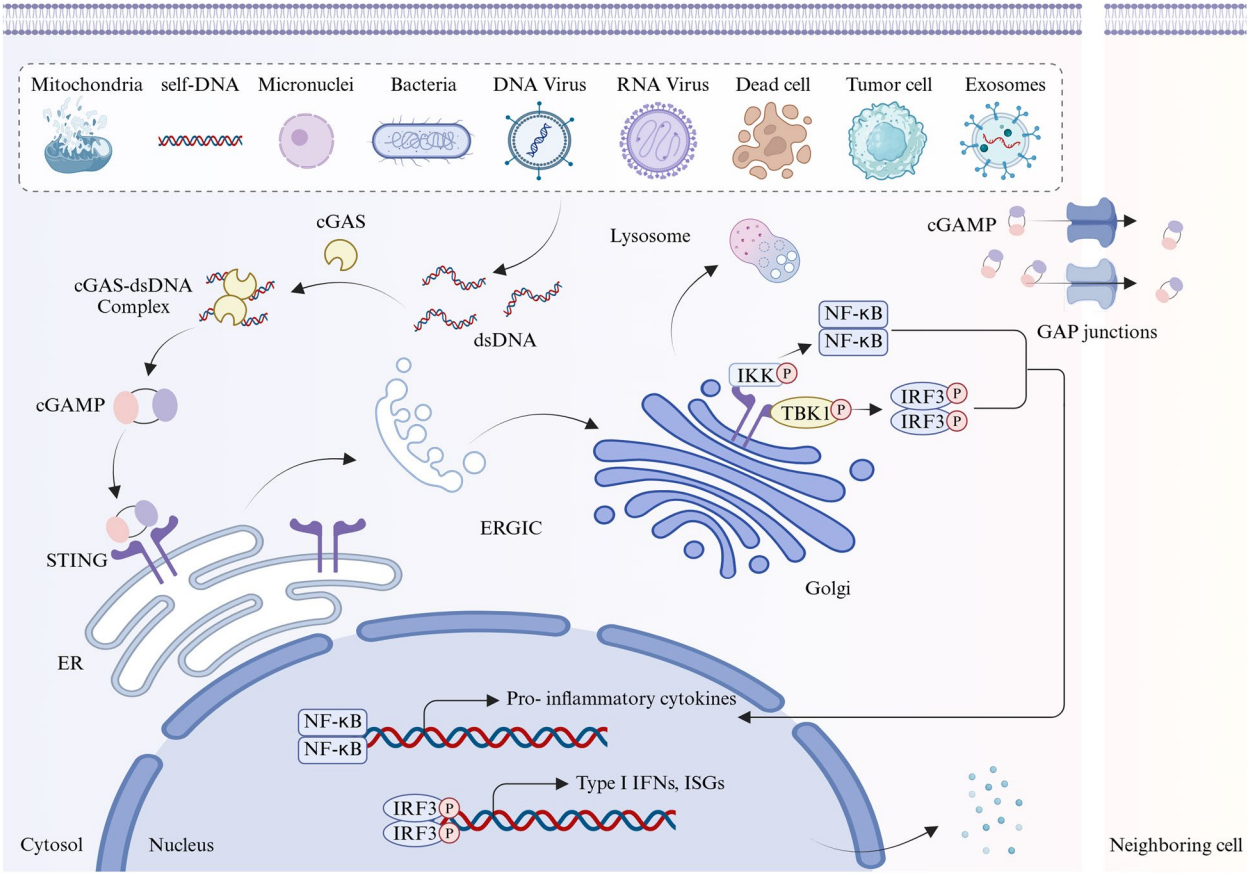

Fig. 2 Overview of the molecular mechanisms of the cGAS-STING signal pathway. The activation of the cGAS-STING signaling begins with the detection of abnormal dsDNA within the cell. Initially, dsDNA binds to cGAS, triggering its enzymatic activity and the production of 2′3′-cGAMP. Subsequently, cGAMP binds to STING on the ER membrane, inducing conformational changes that result in STING oligomerization and translocation to the ERGIC and Golgi apparatus. This change leads to the activation of signaling molecules such as TBK1 and IRF3, which enter the nucleus and initiate the transcription of immune factors like interferons, ultimately initiating the body's immune response to combat infection and damage

IFN response elements, inducing extensive transcription of downstream type I interferons (IFN-I) and interferon-stimulated genes (ISGs), thus triggering IFN-I-mediated immune responses [92]. Additionally, STING can also phosphorylate IκB kinase (IKK), causing the release of nuclear factor kappa-B (NF-κB) into the nucleus, activating the classical NF-κB signaling pathway, and inducing the expression of genes such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-1β, triggering a broad immune response [93].

cGAS-STING-mediated autophagy represents the primitive and highly conserved function of this pathway [94]. Upon binding with cGAMP, STING buds from the ER to form COPII vesicles, forming the ER-Golgi intermediate compartment (ERGIC). The ERGIC-containing STING serves as a membrane source for microtubule-associated protein 1 light chain 3 (LC3) lipidation, promoting the formation of autophagosomes [95, 96]. In contrast, autophagy can feedback-regulate the activity of this pathway as well [97]. In addition to negatively regulating STING signaling by interfering with the assembly of STING-TBK1-IRF3 or STING degradation, autophagy prevents STING activation by delivering cytoplasmic DNA to lysosomal degradation [95, 98, 99]. The reciprocal regulation between the cGAS-STING pathway and autophagy helps clear damaged organelles, abnormal proteins, and accumulated dsDNA in the cytoplasm, suppressing unnecessary inflammatory responses and supporting cellular homeostasis.

Crosstalk between cGAS-STING and mtDNA

The interaction between cGAS-STING and mtDNA and its involvement in disease pathogenesis has long been a focal point of research. A pivotal discovery linking mtDNA to the cGAS-STING pathway demonstrates that mtDNA stress is an intrinsic trigger of antiviral

responses. Specifically speaking, viral infection can lead to abnormal mtDNA escape into the cytosol, where it binds to cGAS and promotes STING-IRF3-dependent signaling, mediating antiviral innate immunity [100]. Other studies have also provided evidence of mtDNA colocalization with cGAS and triggering inflammatory damage under specific conditions [40, 101]. Sliter et al. presented compelling findings connecting mtDNA-STING signaling to neurodegenerative diseases, showing that mitochondrial stress induced by mtDNA mutations triggers a STING-IFN-I response in a PD mouse model lacking Parkin or PINK1 [102]. Furthermore, the release of mtDNA is related to the mitochondrial localization of neuropathological proteins, which may impair the integrity and function of the mitochondrial membrane. A critical study has reported that the mitochondrial localization of tau protein triggers mtDNA leakage and cGAS activation in microglia treated with tau fibrils, diminishing cognitive resilience through decreasing the neuronal transcriptional network of myocyte enhancer factor 2c (MEF2C) [103]. A similar mechanism was revealed in a parallel study, where the mitochondrial translocation of transactive response DNA binding protein of 43 kDa (TDP-43) drives mtDNA release into the cytoplasm, activating the cGAS-STING pathway in ALS models [19]. These studies together demonstrate the interaction of mtDNA with the cGAS-STING and its downstream pathways, providing persuasive evidence that mtDNA escaping into the extramitochondrial space can be sensed by cGAS.

Further in-depth research has established the link between mitochondrial stress in neurons and neuroinflammation. After ischemia–reperfusion injury, ox-mtDNA activated the cGAS-STING pathway within neurons, and restricting the release of ox-mtDNA into the cytoplasm downregulated p-STING expression levels in both neurons and microglia [104]. Other research has reported that neurons could release vesicles containing mtDNA into the extracellular space, which can be engulfed by neighboring microglial cells [105–108]. Additionally, transfection of extracted mtDNA into microglia upregulated the expression of IFN-β which was significantly inhibited upon cGAS knockout [109], thus cGAS in microglia may also be activated by mtDNA released from other cells. Based on these results, we cautiously propose that stressed neurons can release mtDNA and other pro-inflammatory factors into the extracellular space under various harmful conditions, and this displaced mtDNA may then be recognized by nearby microglia or astrocytes, consequently activating cGAS-STING signaling in these immune cells and exacerbating neuroinflammation. Unfortunately, direct evidence for this process is still lacking in AD. If further validated, targeting this pathway may hold even greater promise.

The role of the mtDNA-cGAS-STING pathway in AD

AD is a neurodegenerative disease with an insidious onset, caused by the interaction of genetic and environmental factors [110]. Despite extensive research, its pathogenesis remains elusive. Emerging evidence suggests that mitochondrial disorders and innate immune responses play crucial roles in the development of AD [7, 111]. Specifically, numerous adverse factors, including elevated levels of pathogenic proteins in AD, could destabilize the neuronal mitochondrial genome [112, 113], leading to mitochondrial dysfunction, ultimately triggering the release of disrupted mtDNA into the extramitochondrial space to initiate a series of immune responses [114]. These maladaptive neuroinflammatory activities in the CNS are generally considered to exacerbate pathological changes and accelerate the rate of AD-related cognitive decline [115, 116]. Furthermore, several AD-related risk genes have been implicated in inflammation. As described by He et al., among the 50 AD-related risk loci identified through genome-wide association analysis (GWAS), more than half were significantly enriched or specifically expressed in immune cells, particularly microglia and macrophages, such as Age and apolipoprotein E (*APOE*), triggering receptors expressed on myeloid cells 2 (*TREM2*), and ATP-binding cassette subfamily A (*ABCA*) [117]. More importantly, the cGAS-STING signaling, a pivotal DNA-sensing pathway, links cytoplasmic mtDNA to sterile inflammation and the body's innate immune system, and its activation has been identified across multiple cell types in AD brains [118]. Overall, mtDNA-cGAS-STING activation in AD highlights the intricate interplay between mitochondrial dysfunction and neuroinflammation (Fig. 3). Elucidating the molecular mechanisms of this immune-inflammatory signaling pathway holds immense promise for developing novel therapeutic interventions to mitigate the devastating impact of AD on both individuals and society as a whole.

mtDNA disturbances in AD

Endogenous neuroprotection and repair within the body rely on the health of the mtDNA, whose turbulence inevitably leads to various AD pathological changes, including the abnormal aggregation of pathological amyloid-β (Aβ) plaques [119, 120] and hyperphosphorylated tau protein [121], impaired synaptic transmission and plasticity [122], cholinergic dysfunction [123], and neuroinflammation [124]. For example, mtDNA mutations in mice lead to an increase in Aβ42 levels and Aβ42 plaque density, and the accumulation of amyloidosis is caused by a decrease in the content of Aβ clearance enzymes, rather

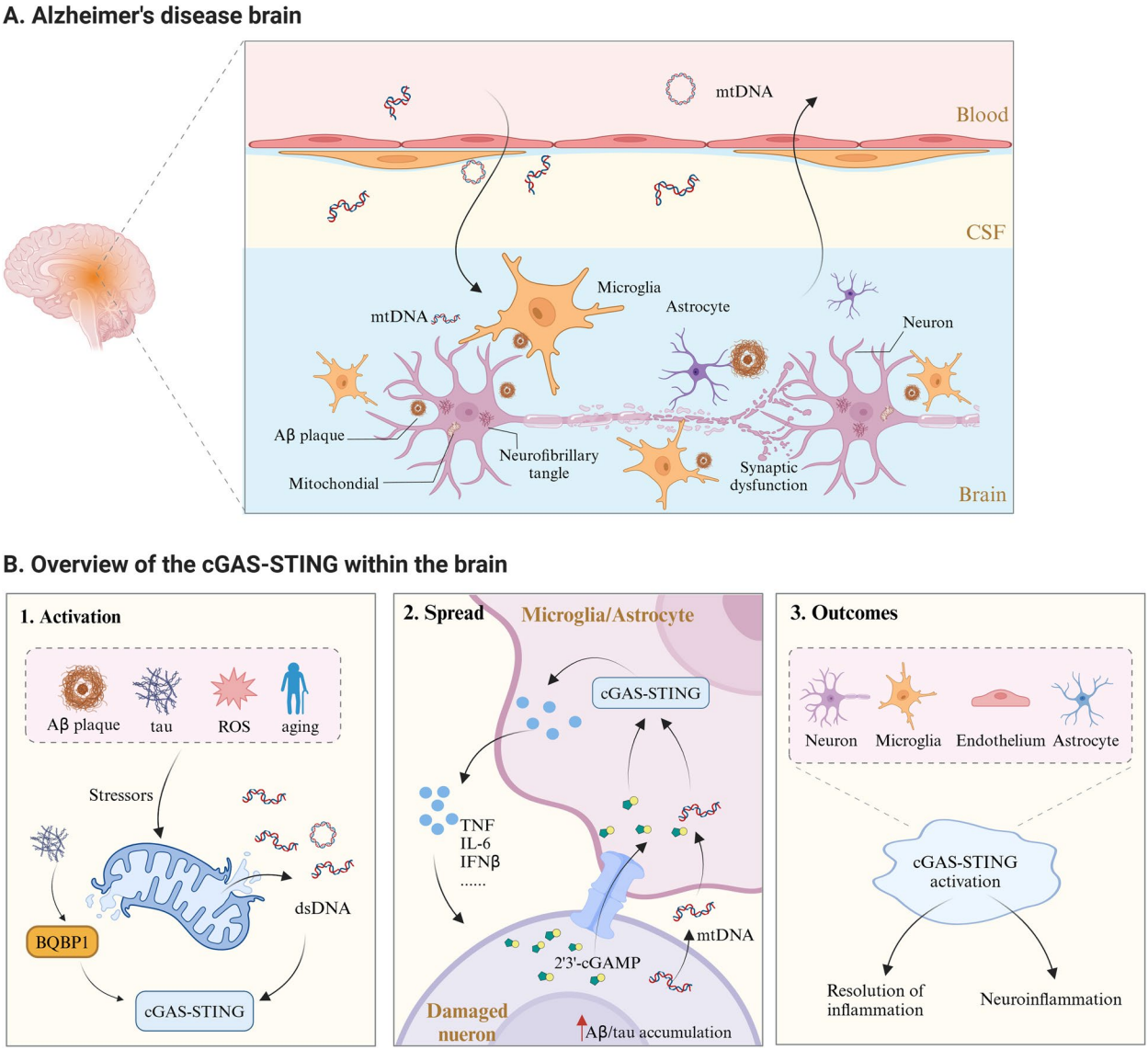

Fig. 3 mtDNA-cGAS-STING signal pathway and neuroinflammation in AD. **A**. In the AD brain, the neurotoxic effects of primary pathological proteins, such as Aβ plaques and neurofibrillary tangles. The overwhelmed mitochondria of injured neurons release mtDNA into the extramitochondrial space, activating immune cells and forming a neuroinflammatory microenvironment in the CNS. **B**. The activation of the mtDNA-cGAS-STING pathway in the brain of AD. Firstly, various adverse factors in AD, such as Aβ plaques, hyperphosphorylated tau, ROS, and aging, stimulate the release of mtDNA from mitochondria in neurons. This mtDNA, along with AD pathological proteins, initiates the cGAS-STING pathway through multiple mechanisms. Secondly, cGAMP spreads through gap junctions in neurons and various glial cells, leading to the release of a series of cytokines by activated glial cells, and modulating neuronal inflammation. Ultimately, the activation of cGAS-STING would lead to complex outcomes. Various cell types in the brain play a role in the activation of this pathway, which, on one hand, can alleviate brain inflammation to some extent, while, on the other hand, its excessive activation forms a widespread neuroinflammatory network, exacerbating brain damage and promoting disease progression

than an increase in Aβ production [125]. This decrease in Aβ clearance is likely due to energy supply disruption connected to mtDNA damage. Consistently, Scheffler et al. confirmed that mtDNA polymorphisms, such as mutations affecting oxidative phosphorylation or the tricarboxylic acid cycle, can cause reduced ATP levels and ATP-driven microglial activity, resulting in increased Aβ aggregation [126]. These studies suggested that mtDNA disruption exacerbates AD pathology by impairing mitochondrial function. In turn, mtDNA is susceptible to attacks from these destructive changes, further exacerbating mitochondrial injury [127, 128]. Specifically, Aβ

can be transported to mitochondria through the translocase of the outer membrane (TOM) and localize to the mitochondrial cristae [129, 130], impairing oxidative phosphorylation pathways, causing mtDNA oxidative damage and DNA double-strand breaks (DSBs) [131]. This vicious cycle between mitochondrial defects and AD pathological impairment [132, 133] accelerates the rate of cognitive decline.

Several AD-related studies have provided abundant evidence to indicate the importance of mtDNA disturbances, primarily oxidative damage, mutations, and methylation transfer [134]. In the brain tissue samples from APPswe/PS1dE9 (APP/PS1) transgenic mouse model and AD patients, expression levels of genes necessary to mitochondrial replication and energy metabolism, including the peroxisome proliferator-activated receptor gamma coactivator 1 alpha (*PGC-1α)*, mitochondrial transcription factor A (*TFAM),* and neurogenic differentiation factor-6 (*NEUROD6*), are significantly downregulated [135, 136], indicating a pronounced mtDNA maintenance defect in AD. Similarly, the oxidized base level of mtDNA in the brains of postmortem AD individuals has been shown to be markedly higher than that in an age-matched control group, and is approximately tenfold that of nuclear DNA (nDNA) [137]. Additionally, Chang et al. found a greater frequency of mtDNA point mutations in the hippocampal region of patients with AD, whereas the mtDNA (4977) and deletion mutation did not increase [138]. However, Hamblet et al. indicated that mtDNA delta 4977 in the temporal lobe cortex of postmortem AD brains was elevated 6.5 folds [139]. Notably, lower levels of mtDNA mutations have also been observed in patients with AD [124], which may be related to neuronal death and loss during AD progression. In addition, the degree of mtDNA methylation in AD remains highly uncertain [140, 141], possibly due to methodological differences among studies. In conclusion, current research on mtDNA abnormalities in AD has not reached a consensus, and mtDNA disorders exhibit significant heterogeneity. In the future, it will be necessary to interpret the role of mtDNA in AD pathogenesis using improved detection techniques, increased sample sizes, and other feasible approaches.

Alterations in mtDNA content in AD remain controversial [142–144] (Table 1). Increased levels of cytoplasmic mtDNA have been observed in the brains of 5xFAD mice compared with age-matched wild-type mice [145]. In line with this, Laura et al. reported elevated mtDNA counts in the CSF of patients with AD compared to those in normal individuals, albeit with considerable inter-individual heterogeneity [146]. Nevertheless, some studies have documented a reduction in mtDNAcn in the brain of AD patients [143, 144], as well as decreased levels of free mtDNA in the CSF of patients with preclinical AD [147]. A possible explanation is reduced energy metabolism or abnormal mitochondrial function in AD, which is reflected by mtDNAcn to some extent. While most studies have indicated a close relationship between abnormal mtDNA levels and AD pathology, determining whether changes in mtDNA content are causally related to the onset of AD and the specific mechanisms by which mtDNA levels affect AD pathogenesis remain significant challenges.

Direct evidence of the activation of cGAS-STING in AD

Although studies on the relationship between the cGAS-STING pathway and AD are currently limited, evidence of the activation of this pathway has been found in patients with AD and multiple AD models (Table 2). Increased interactions between dsDNA, RNA–DNA hybrids, and cGAS have been observed in AD patient-derived iPSCs [166], 5xFAD mice [145], or human AD fibroblasts [167]. Ferecskó et al. discovered that the expression levels of STING in neurons and endothelial cells were significantly elevated in CNS tissues extracted from AD patients [168]. Consistently, the phosphorylation levels of STING, TBK1, p-65, and IRF3 were found to be upregulated in the prefrontal cortex of AD patients [145]. Further studies demonstrated that cGAS gene deletion in 5xFAD mice alleviated cognitive impairment, Aβ aggregation, neuroinflammation, and cholinergic neuron damage; STING inhibitors also sustainably ameliorated AD pathogenesis, which may be partially attributable to the inhibition of neurotoxic A1 astrocytes [117, 145, 167].

Interestingly, two studies based on the APP/PS1 mouse model revealed reduced activity of the cGAS-STING pathway, whereas most research reports its activation (Table 2). Wang et al. found that the expression levels of cGAS and STING were significantly downregulated in the cardiomyocytes of APP/PS1 mice [175], despite the large aggregation of cytoplasmic mtDNA. Another study also observed a downward trend in STING expression levels in the APP/PS1 model compared to wild-type mice, although the differences were insignificant [179]. These contradictory results may be potentially due to differences in genetic backgrounds, stages of disease progression, and specific experimental conditions. Findings on this pathway derived from studies based on the APP/PS1 model should be carefully evaluated. In addition, STING in the Golgi apparatus was found to be nearly depleted in AD patients in a study by Nelson et al. [172]. A possible reason for this may be the prolonged activation of the cGAS-STING in the brain tissue, which has exhausted related components, and such prolonged activation may be mediated by the accumulated mtDNA and

Table 1 Changes in mtDNA levels in clinical studies of AD

Sample type	Tissue/Cell Type	Sample size	Country	Technique	Trend	Disease Stage	Reference
Brain	-	AD/control: 282/351	UK	Exome sequencing	Decrease	AD	[143]
Brain	Hippocampal pyramidal neurons	AD/control: 10/9	US	qPCR	Decrease	AD	[148]
Brain	Frontal cortex	AD/control: 12/7	Spain	RT-PCR	Decrease	AD	[149]
	Hippocampus and cerebellum				No change	AD	
Blood	-	AD/control: 17/11			No change	AD	
Brain	Frontal cortex	AD/control: 23/40	US	qRT-PCR	Decrease	AD	[150]
Brain	Dorsolateral prefrontal cortex	AD/Non AD: 251/116; 57/30	US	WGS	Decrease	AD	[144]
	Posterior cingulate cortex	AD/Non AD: 45/21			Decrease		
	Cerebellum	AD/Non AD: 141/101			No change	AD	
	Temporal cortex	AD/control: 89/51			Decrease	AD	
	Frontal pole	AD/control: 205/132			Decrease	AD	
Brain	Temporal cortex	AD/control: 10/10	Brazil	ddPCR	Decrease	AD	[151]
	Cerebellum	AD/control: 10/10			No change	AD	
Brain	CSF	Symptomatic AD/ Asymptomatic patients at risk of AD: 13/10 (study cohort a), 20/9 (study cohort b), 17/19 (validation cohort)	Spain	qPCR; ddPCR	Decrease	Symptomatic AD	[147]
Brain	CSF	AD patients progressed faster/control: 30/49	Germany	ddPCR	Decrease	AD patients progressed faster	[152]
		AD patients progressed lower/control: 16/49			No change	AD patients progressed lower	
Brain	CSF	AD/MCI/Preclinical AD/control: 58/42/20/140	Spain	ddPCR	Increase	Preclinical AD, MCI and AD	[146]
Brain	Pyramidal neurons	AD/old control/young control: 27/12/8	-	In situ hybridization	Increase	AD	[153]
Blood	Leukocyte	AD/control: 82/82	Tianjin, China	qRT-PCR	Decrease	AD	[154]
Blood	CD4 + , CD19 + and CD56 + peripheral lymphocytes	Early-stage AD/ late-stage AD/control: 30/30/30	Turkey	RT-PCR	Decrease	Early-and late-stage AD	[155]
	CD8 + peripheral lymphocytes			RT-PCR	Decrease	Late-stage AD	
Blood	Plasma	Cognitive impaired/ control: 11/35	US	RT-PCR	Increase	Cognitive impaired	[156]
	Buffy coat				Decrease		
Brain	Parietal cortex	AD/MCI/control: 24/6/16	UK	qRT-PCR	Decrease	MCI and AD	[157]
Blood	Leukocyte	Cognitive impaired/ control: 29/78	Korea	qPCR	Decrease	Cognitive impaired	[158]
Blood	Leukocyte	Cognitive dysfunction/control: 125/61	Korea	RT-PCR	Decrease	Cognitive dysfunction	[159]
Blood	whole blood	AD/MCI/control: 28/31/28	UK	qRT-PCR	No change	MCI and AD	[142]
Brain	Dorsolateral prefrontal cortex	-	US	WGS	Decrease	MCI and AD	[160]

Table 1 (continued)

Sample type	Tissue/Cell Type	Sample size	Country	Technique	Trend	Disease Stage	Reference
Blood	Buffy coat	AD/MCI/control: 31/72/149 (Mexican American)	US	qPCR	Decrease	AD	[161]
		AD/MCI/control: 63/28/129 (Non-Mexican American)			Increase	MCI	
	Plasma	AD/MCI/control: 38/82/91 (Mexican American) AD/MCI/control: 67/34/142 (Non-Mexican American)			No change	MCI and AD	
Blood	Leukocyte	AD/control: 600/601	Taiwanes, China	RT-PCR	Decrease	AD	[162]
Brain	-	-	US	WGS	Decrease	AD	[163]
Brain	Frontal cortex	AD/control: 13/25	US	qRT-PCR	Decrease	AD	[164]
Blood	Peripheral blood mononuclear cell	AD/MCI/control: 20/24/30 (Spanish cohort), 248/70/276 (Italian cohort)	Spanish, Italian	RT-PCR	Decrease	MCI and AD	[165]

other dsDNA. However, it remains unclear whether the prolonged activation of this pathway truly exists in AD. Additionally, the threshold dose of dsDNA that triggers neuroinflammation and cellular damage, as well as the activation effects of different types of dsDNA, has yet to be fully defined. Overall, these changes reflect the plasticity of the pathway under different conditions to some extent and the potential protective effects of modulating this pathway in AD. Based on the existing evidence, understanding the role of the cGAS-STING in AD requires considering the composite effects of these factors, and how to balance the pathway to develop more effective therapeutic strategies.

Activation of cGAS-STING is associated with mtDNA in AD

Xie et al. previously linked the activation of the cGAS-STING pathway to mtDNA in AD. In their research, mtDNA and 2'3'-cGAMP levels in primary microglia, neurons, and astrocytes were found to be significantly increased following treatment with oligomeric human Aβ42 peptides [145]. Similarly, Wilkins et al. demonstrated that mitochondrial lysates or mtDNA injected into the mouse hippocampus could act as a DAMP to induce inflammatory responses and affect AD-related biomarkers [182]. Furthermore, Hou et al. found that nicotinamide riboside (NR) supplementation can rescue abnormal mitochondrial autophagy and reduce cytoplasmic DNA levels in the APP/PS1 mouse model, thereby reducing the cGAS perception of mtDNA [167]. In addition, Zhao et al. suggested that the mtDNA released by neurons activates the cGAS-STING pathway in adjacent microglia, astrocytes, and other neuronal cells [183], but further research is needed to confirm this opinion in AD. Overall, these studies provide preliminary evidence that extracellularly released mtDNA likely facilitates communication between various types of neuronal cells, promotes the propagation of neuroinflammation, and exacerbates the inflammatory microenvironment.

The relationship between cGAS-STING and the core pathological mechanism of AD

Hyperactivation of cGAS-STING and the aggregation of Aβ proteins are adverse factors in AD, and their interactions accelerate the pathological progression of AD [176]. Acker et al. found that the activation of cGAS-STING upregulated autophagy and induced amyloid precursor protein-C-terminal fragment (APP-CTF) accumulation [173]. Furthermore, p-STING primarily colocalized with the activated microglia marker CD68 around Aβ plaques in 5×FAD mice [145], which may be related to ER and mitochondrial stress induced by the accumulation of neurotoxic proteins. In contrast, inhibition of the cGAS-STING and its downstream signaling could significantly alleviate Aβ toxicity [89, 117, 173]. These studies emphasize the importance of the cGAS-STING pathway in the neurotoxic process induced by Aβ aggregation and enrich the pathogenic mechanisms of Aβ as well.

The interaction between cGAS-STING and aberrantly aggregated hyperphosphorylated tau protein also contributes to AD development. Sequencing results from

Table 2 Research evidence on the correlation between the cGAS-STING pathway and AD

Model	Human sample	cGAS-STING activity	dsDNA levels	Intervention	Changes in dsDNA, cGAS-STING after Intervention	Intervention effect	References
APP/PS1 mice; Aβ induced HMC3 human microglial cells	-	Upregulated cGAS, STING	Increased cytosolic mtDNA level	NAD^+	Decreased cytoplasmic mtDNA, cGAS, STING levels	Reduced neuroinflammation; improved cognition impairment and synaptic plasticity; prevented cellular senescence; promoted the protective microglial phenotype	[167]
5xFAD mice	Hippocampal region of AD patients	Upregulated cGAS, STING	Increased cytosolic mtDNA level	*Cgas*−/−; RU.521; H-151	Suppressed the activation of the cGAS-STING pathway	Alleviated cognitive impairment, Aβ pathology, neuroinflammation; inhibited neurotoxic A1 astrocytic phenotype in microglia	[145]
APP/PS1 mice	-	Upregulated cGAS, STING	Increased cytosolic dsDNA level	Tetrahydroxy stilbene glycoside	Decreased cGAS, STING; alleviated the accumulation of cytosolic DNA	Ameliorated neuroinflammation; improved cognition impairment; inhibited the polarization of microglia toward M1-type	[169]
5×FAD mice	-	Upregulated cGAS, STING	-	Cgas deletion; H-151	-	Suppressed the formation of neurotoxic A1 astrocytes; decreased oligomeric Aβ-induced neuronal toxicity	[170]
5xFAD mice	AD patients	Upregulated cGAS, STING	-	Microglia-specific cGAS knockout	-	Alleviated Aβ-induced cognitive impairment; limited plaque formation; reduced the levels of dystrophic neurites	[117]
APP/PS1 mice; sporadic AD patients derived-human skin fibroblast cell line	-	Upregulated cGAS, STING	Increased mtDNA level	NR	Elevated the cGAS-STING was normalized; reduced cytoplasmic DNA levels	Increased mitophagy; reduced neuroinflammation and cellular senescence; improved cognition and behavior; promotes anti-inflammatory microglial polarization	[171]
-	Temporal lobe of AD patients	Impaired cGAS-STING-interferon signaling	Increased dsDNA damage	-	-	-	[172]
PLD3 deficient SH-SY5Y cells	-	Upregulated cGAS, STING	Increased mtDNA level in lysosomes and cytoplasm	APP knockout; H151	Lowered STING activation;	Normalized APP-CTF levels and cholesterol biosynthesis	[173]

Table 2 (continued)

Model	Human sample	cGAS-STING activity	dsDNA levels	Intervention	Changes in dsDNA, cGAS-STING after Intervention	Intervention effect	References
-	AD patients, dapsone, and anti-AD drug users in Hansen subjects	-	-	Dapsone (cGAS-STING pathway inhibitor)	-	Prevented AD exacerbation	[174]
APP/PS1 mice	AD patients	Downregulated cGAS, STING	Increased cytosolic mtDNA level	Melatonin	Promoting the cGAS-STING signaling; Ameliorated cytosolic mtDNA accumulation	Ameliorated APP/PS1-induced changes in cardiac geometry and function, apoptosis, mitochondrial integrity, and mitophagy	[175]
AD patient derived-iPSCs	-	Upregulated cGAS, STING	Increased cytosolic RNA–DNA hybrids level	c-Jun inhibition	Rescue RNA–DNA hybrid formation and the cGAS-STING activation	Rescued neuronal death and the impaired neurogenesis phenotype in AD progenitors	[166]
Aβ induced microglia	-	Upregulated cGAS, STING	-	RU.521; C-176; IFITM3 Knockdown	Decreased cGAS, STING	Suppressed the M1-like polarization of microglia; reduced neuroinflammation	[176]
APP/PS1 mice; Aβ induced HT22, N2a and SK-N-BE cell lines	-	Upregulated STING	Increased mtDNA leakage	Knocking out STING	Decreased STING	Inhibited Aβ1–42 and mtDNA induced neuron degeneration and cognitive impairment	[177]
STZ-treated HT22 murine hippocampal neurons; ICV-STZ rats	-	Upregulated STING	-	Silibinin	Decreased STING	Promoted survival of STZ-treated HT22 cells; ameliorates the cognitive impairment and anxiety/depression-like behavior of ICV-STZ rats; reduces STING-mediated neuroinflammation	[178]
P301S transgenic mice; tau induced microglia	AD patients	Upregulated cGAS, STING	Increased cytosolic mtDNA level	*Cgas* loss; TDI-6570	-	Restored synaptic integrity, plasticity and memory	[103]
APP/PS1 mice	-	Downregulated STING	-	cGAMP	Upregulated the expression of STING	Ameliorates cognitive deficits; improved pathological changes; decreases Aβ plaque load and neuron apoptosis	[179]

Table 2 (continued)

Model	Human sample	cGAS-STING activity	dsDNA levels	Intervention	Changes in dsDNA, cGAS-STING after Intervention	Intervention effect	References
App^{NL-G-F}/hTau double-knock-in mice; *APOE* ε4 human iPSC-derived microglia; Primary microglia treated with Aβ and tau	-	Upregulated cGAS, STING	Increased cytosolic mtDNA level	H-151; SN-011; STING knockout	Decreased STING	Reduced a wide range of AD pathogenic features; reduced gliosis and cerebral inflammation; prevented memory loss	[180]
APOE4-R47H female tauopathy mice	-	Upregulated cGAS, STING	Increased cytosolic mtDNA level	-	-	-	[181]

The text lists the research evidence on the causal relationship or correlation between AD and the cGAS-STING pathway. *PLD3* Phospholipase D3, *STZ* Streptozotocin, *ICV* Intracranial volume, *iPSC* Induced pluripotent stem cell, *FAD* Familial Alzheimer's disease, *APP/PS1* APPswe/PS1dE9, NAD^+ Nicotinamide adenine dinucleotide, *NR* Nicotinamide riboside, *RU.521* One of the cGAS inhibitors, *H-151* One of the STING inhibitors, *C-176* One of the STING inhibitors, *IFITM3* Interferon-induced transmembrane protein 3

hippocampal tissue in a tau-induced disease model revealed elevated levels of cGAS and STING, while genetic ablation of cGAS in mice with tauopathy alleviated the activation of IFN-I response in microglia, without altering the pathological tau load in the brain. Additionally, pharmacological inhibition using TDI-6570, a non-toxic, brain-penetrant cGAS inhibitor, enhanced the neuronal MEF2C transcriptional network in the tauopathy mouse model, restoring synaptic integrity, plasticity, and memory [103]. Another recent study demonstrated that pharmacological inhibition of STING significantly reduces various pathological tau phosphorylation events in the AppNL-G-F/hTau double-knockin mouse model, further supporting the role of the cGAS-STING pathway in tau pathologies [180]. These studies revealed the critical role of the cGAS-STING pathway in AD, especially in its interaction with Aβ and tau. The modulation of this pathway may reduce the deposition of these pathological proteins, inhibit neuroinflammation, and protect neuronal and synaptic functions.

The relationship between the cGAS-STING pathway and APOE genotype

APOE ε4 is the strongest genetic risk factor for late-onset sporadic AD, exacerbating neurodegeneration induced by tau [184]. This process is partially attributed to a crucial immune hub, which involves the activation of the interferon pathway in microglia and interactions with cytotoxic T cells [185, 186]. Recent studies indicate that cGAS-STING plays a significant role in this context as well, further linking innate immunity to neuroinflammatory responses in AD. Chung et al. found that APOE ε4 allele, like Aβ and tau, upregulated cGAS and STING expression in microglia. The knockout or pharmacological inhibition of STING reversed the reactivity of APOE ε4 human iPSC-derived microglia, significantly reducing the Aβ burden and tau hyperphosphorylation while preserving memory functions in AppNL-G-F/hTau-dKI mice [180]. In addition, the R47H variant of the TREM2 and female sex are risk factors for sporadic AD. A study by Carling et al. found that APOE ε4 and R47H amplify the tau-induced microglial cGAS-STING-IFN-I responses in female mice, worsening neurodegeneration through upregulated cGAS and BAX-dependent microglial senescence, suggesting that enhanced IFN-I signaling under APOE ε4 and R47H backgrounds could be an important pathological mechanism in AD [181]. Specific APOE mutations, such as the R136S mutation on APOE3, could reduce tau-related pathological burden by inhibiting the cGAS-STING-IFN signaling pathway, and treatment with cGAS inhibitor prevented tau-induced synaptic loss in E3/P301S mice [185, 187]. These findings emphasize not only the importance of the APOE-activated cGAS-STING pathway in tau pathology but also the role of microglia in this inflammatory process. Modulating the cGAS-STING pathway may provide new strategies for developing therapies against AD, especially in carriers of the APOE ε4 allele.

Neuroinflammation induced by cGAS-STING and AD

Neuroinflammation is another significant feature of AD pathogenesis, involving aberrant activation of the innate immune system [188]. This effect is to some extent dependent on the disruption of the cGAS-STING pathway in different cells within the brain, especially in immune cells [189]. Although several types of neural cells can express cGAS and STING, microglia have been found to be the primary contributors to this pathway [117, 190, 191], which partially explains why they have been identified as major participants in neuroinflammation. Overall, abnormal activation of the cGAS-STING axis in diverse neuroglial cells is significant in the neuroinflammatory and neurodegenerative processes, particularly in microglia. Notably, moderate activation of this pathway may exert neuroprotective effects by suppressing inflammation. Evidence suggests that cGAMP treatment could activate the STING-IRF3 pathway to upregulate TREM2 expression, alleviating cognitive deficits and pathological changes in APP/PS1 transgenetic mice [179]. Another research has reported that ganciclovir can exert anti-inflammatory effects by mediating low therapeutic levels of IFNs, and this effect is STING-dependent [192]. Thus, the effects of cGAS-STING pathway activation vary, potentially depending on the differences in cell types and the extent of its activation. However, how to appropriately activate this pathway to achieve similar protective effects remains unclear. Further research is required to explore the balance between the anti-inflammatory and pro-inflammatory responses of this pathway in AD to achieve optimal neuroprotection.

The cGAS-STING pathway primarily induces neuroinflammation by regulating the expression of ISGs in inflammatory diseases [193, 194], including AD. Although the basal level of ISG mRNA in the CNS is generally much lower than in peripheral tissues, the brain is highly sensitive to IFN effects [195, 196]. In AD mouse models, pathological Aβ protein leads to a significant increase in ISG mRNA expression levels in the brain, and selective IFN receptor blockade effectively reduces persistent microgliosis and synaptic loss. Recent studies have also found that innate immune stimulation in neurons can drive seeded tau aggregation through the IFN-I response [197]. In clinical AD patients, the IFN pathway is also markedly upregulated and significantly correlated with disease severity and complement activation [198]. Additionally, the IFN-I produced by cGAS-STING

pathway can induce a series of inflammatory responses by binding to its respective receptors in microglia, astrocytes, and neurons [199]. Then, these activated microglia secrete cytokines and chemokines, such as IL-1 and TNF-α, causing neurotoxicity through communicating with neurons [200]. Concisely, the cGAS-STING-IFN-I axis serves as an important mediator of neuroinflammation, forming a sophisticated regulatory network that bridges neuroglia and neurons in the CNS, leading to neuronal loss, and ultimately accelerating the onset of AD.

Interaction between Cellular Senescence and cGAS-STING in AD

The interplay between cGAS-STING and cellular senescence is considered another crucial pathological process that accelerates AD progression [201, 202]. A recent study has shown that aged microglia, compared to young microglia, exhibit an increased mtDNA burden in the cytosol. This triggers the activation of the cGAS-STING pathway and subsequent aging-related reactive microglial transcriptional states, suggesting that the cGAS-STING pathway is a driving force behind age-related inflammation [203]. Consistently, the accumulation of senescent cells, along with cGAS activation and STING homodimer formation, has been observed in various types of neural cells during aging [204–207]. In the APP/PS1 mouse model, cGAS and STING expression levels were higher in aged mice compared to younger mice [167]. After cGAS knockout in mouse embryonic fibroblast cells, the rate of cellular senescence significantly slowed and progressed toward immortalization [85]. Another research has shown that blocking cGAS or STING suppressed etoposide-induced cellular senescence [167]. As such, dsDNA released during aging signals through the cGAS-STING pathway, and targeting the cGAS-STING pathway holds considerable promise for slowing AD development by inhibiting the aging process.

One of the important mechanisms through which the interplay of the cGAS-STING pathway and cellular senescence contribute to AD is the activation of the senescence-associated secretory phenotype (SASP) [202], which includes a variety of cytokines, chemokines, and growth factors secreted by senescent cells [208, 209]. These SASPs can recruit immune cells and regulate their activity [207], altering intercellular communication levels, and thus accelerating the aging of senescent cells and their neighboring cells [210, 211]. During aging, the process by which the cGAS-STING induces SASP has been considered to involve LINE-1 (L1), a key component of sterile inflammation and a hallmark of aging. According to research by De Cecco et al., the transcriptional derepression of L1 activates IFN-I responses, sustaining SASP and exacerbating inflammatory senescent phenotypes during cellular senescence, and knocking out cGAS or STING suppresses SASP gene expression in late senescent cells [212]. Other studies have also shown that cGAS or STING inhibition downregulates SASP gene expression in both mouse and human cells [85, 213].

cGAS-STING-mediated senescence is also involved in the release of mtDNA. Specifically, mitochondria exhibit structural abnormalities and accumulate mtDNA in the cytoplasm in aged microglia, which subsequently triggers a cGAS-dependent inflammatory response [203]. Notably, Victorelli et al. discovered an intriguing phenomenon during cellular aging in which a subset of mitochondria undergoes a process called miMOMP, leading to mtDNA translocation into the cytosol to trigger cGAS-STING activation [33]. These findings suggested that cGAS-STING is a crucial molecular link between various types of DNA damage, mitochondrial dysfunction, and aging. More research is needed to fully understand the intricate relationships between them and the precise molecular mechanisms underlying these connections, thus providing valuable evidence for the development of more effective targeted drugs for AD.

The involvement of cGAS-STING in AD depends on microglia

Microglia, traditionally regarded as the resident macrophages of the brain, are involved in various physiological functions, ranging from immune surveillance to synaptic pruning [214]. In AD, microglia play a dual role, that is closely related to their involvement in the metabolic processes of neurotoxic proteins such as Aβ. On one hand, they can release degrading enzymes to degrade Aβ and further clear them through phagocytosis [215]. On the other hand, they further serve as carriers to seed Aβ, promoting its pathological spread throughout the CNS [216]. In turn, Aβ accumulation within the brain leads to the phenotypic shift of microglia, releasing neuroinflammatory substances and further contributing to neurotoxicity [176, 217]. Currently, the aberrant activation of cGAS-STING in microglia is believed to ultimately lead to neuronal dysfunction [117]. Modulating the activity of this pathway in microglia may aid in balancing the neuroprotective and neurotoxic effects, thereby slowing the progression of AD.

In recent studies, microglia have been regarded as the primary contributors to the cGAS-STING activation in AD, which is largely attributed to the relatively high expression levels of these two proteins [103, 170, 218], despite controversies regarding their expression levels across diverse cell types. Although Aβ oligomers can trigger cGAS activation in many types of neural cells, a more specific STING-IFN response is triggered in microglia,

rather than in neurons and astrocytes [145]. Additionally, moderate expression levels of cGAS in neurons and oligodendrocytes were observed in another study, with low levels in astrocytes and endothelial cells [117]. Overall, cGAS-STING is largely not limited to a single cell type but encompasses a spectrum of cellular responses within the brain during AD. In addition to focusing on the complex role of this pathway in microglia, further exploration is required to understand the specific mechanisms in different cell types and how these cells communicate with each other, thus collectively slowing the development of AD.

Microglial neuroprotection or neurotoxicity depends on their phenotype and function to some extent (Fig. 4) [188], which can be regulated by the cGAS-STING pathway. AD-related research has focused mainly on

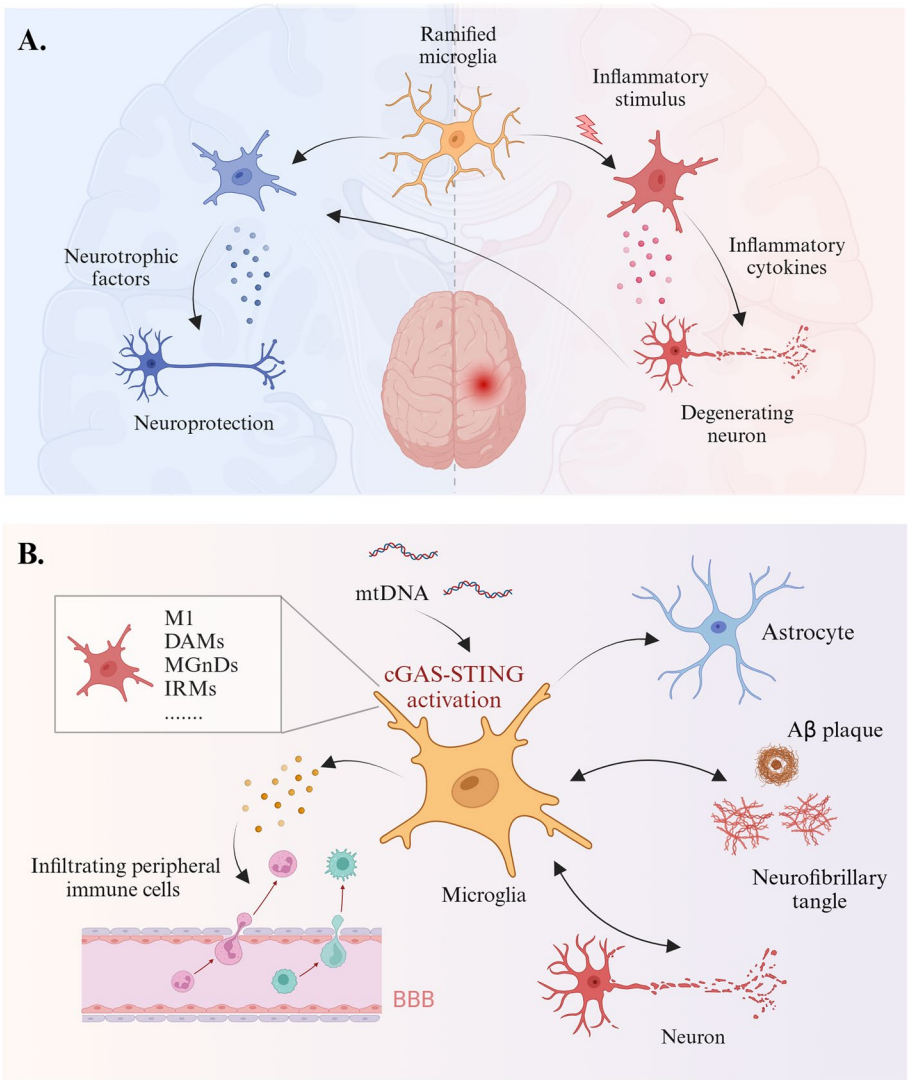

Fig. 4 Microglia and the cGAS-STING pathway in AD. **A** The dual role of microglia in the CNS. Under physiological conditions, ramified microglia survey the brain microenvironment through their processes, sensing various damage signals. These highly dynamic cells perform immune surveillance, provide neurotrophic support, promote the establishment and maturation of neural circuits, and clear pathogens or debris, maintaining brain homeostasis. When the brain is challenged by pathogens or subjected to injury, activated microglia release various factors, including pro-inflammatory cytokines and chemokines. These factors help clear pathogens or toxins but may also lead to neuronal dysfunction and damage. **B** Activation of the cGAS-STING pathway in microglia in AD: Microglia are the primary cell type that activate cGAS-STING signaling in the brain. Pathological aggregates, such as Aβ plaques and tau proteins, cause mitochondrial damage and mtDNA release, leading to the activation of the cGAS-STING pathway in microglia, as well as astrocytes. Additionally, microglia secrete cytokines that induce the infiltration of peripheral immune cells, collectively modulating inflammation to alleviate neurodegeneration. However, overactivation of this system results in neuroinflammation, which can lead to neuronal dysfunction

traditional M1 and M2 microglial phenotypes currently [169, 176, 179], although evidence challenging this dichotomy exists. Single-nucleus RNA sequencing has identified other specific activation states in microglia related to cGAS, including interferon-responsive microglia (IRM), disease-associated microglia (DAM), and neurodegenerative microglia (MGnD). IRMs, a subset of microglia enriched with IFN response genes such as *Ifits*, *Stat1*, *Sp100, Trim30a*, and *Parp14* [181, 203], play a crucial role in AD-related neuroinflammation. According to a recent study, IRMs are significantly enriched in APOE4-R47H tauopathy mice [181]. Another research found that the proportion of IRMs increases with age, a process further exacerbated by Aβ deposition [219]. Importantly, the phenotypic transition to IRMs is closely linked to DAMPs and the activation of the cGAS-STING pathway [220]. In the mg-$Cgas^{R241E}$ microglial population, IFN signatures were broadly upregulated, indicating that cGAS activation induces microglia to transition into a distinct IFN-activated state, which in turn promotes neuroinflammation and aging processes [203]. The increase in DAM is another prominent feature in AD [221], and cGAS activation has been found to facilitate the transition of DAM subtypes from a low-activation state (DAM-1) to a high-activation state (DAM-2) [203]. In 5xFAD mice, the absence of cGAS significantly eliminates Aβ pathology-induced DAM markers [117]. However, these findings mainly rely on bulk transcriptomics and single-nucleus RNA sequencing, which may overlook the spatial differences in microglial activation states across different brain regions. The integration of spatial transcriptomics can better reveal the heterogeneity of cGAS-STING-driven microglial phenotypes across different brain regions in AD.

Various receptors expressed in microglia are linked to the activation of this pathway. Polyglutamine-binding protein 1 (PQBP1), an intracellular receptor capable of binding to HIV cDNA [222], has emerged as a participant in tau-mediated cGAS activation. Upon recognition of tau3R/4R, PQBP1 activates cGAS-STING, leading to the induction of NF-κB nuclear translocation. In contrast, depletion of PQBP1 markedly attenuates the recruitment of cGAS and NF-κB-dependent transcription of inflammation genes, thus mitigating inflammation in the brain and cognitive impairment [223]. As such, PQBP1 is a promising novel therapeutic target for AD and other tau proteinopathies. Another relevant receptor is TREM2, a transmembrane immune receptor predominantly expressed in microglia [224]. Xu et al. demonstrated that stimulation of the cGAMP-STING-IRF3 pathway can induce TREM2 expression, which promotes the phagocytosis of Aβ by microglia, and reduces Aβ deposition and neuronal loss, simultaneously attenuating the pathological morphology and cognitive deficits in AD. Therefore, upregulating TREM2 may exert a regulatory effect on the cGAS-STING pathway, potentially mitigating its neurotoxic effects to some extent.

The propagation of inflammatory signals triggered by STING-IFN in the microglia relies on intercellular gap junctions. Gap junction channels serve as vital conduits for intercellular communication, enabling the unrestricted flow of various small molecules and ions between neighboring cells [225]. Ablasser et al. demonstrated that the 2'3'-cGAMP produced by cGAS can exploit gap junctions to establish inflammatory crosstalk between human embryonic kidney cells and murine embryonic fibroblasts [226], and can also be transported between adjacent cells through specific anion channels [227]. In a mouse model induced by high-fat diets, the activation of cGAS-STING and microglia both occurred in the CNS; however, in their neuron-microglia co-culture system, a significant inhibition in cGAS-STING activation and inflammatory crosstalk was observed upon blocking gap junctions [228]. Accordingly, 2'3'-cGAMP produced in neurons can similarly converge into adjacent microglia, triggering the activation of STING-IFN and subsequently producing diverse inflammatory factors [229]. These inflammatory mediators not only stimulate microglia but can also influence other types of cells, such as astrocytes and neurons, thereby establishing a vast inflammatory microenvironment within the brain [230, 231]. The association between gap junctions and AD pathology described by Mei et al. is also noteworthy; in this study, they observed the enrichment of gap junction-forming proteins CX43 and CX30 near Aβ plaques, and blocking these gap junctions slowed pathological progression [232]. To conclude, gap junctions and other channels are likely involved in the exchange of cGAS-STING-mediated inflammatory signals between neurons and glial cells. Exploring the signal transduction mechanisms between neighboring neural cells may help to identify approaches to regulate this process of inflammatory communication, ultimately slowing down or even inhibiting the progression of AD.

Potential therapeutic strategies and future directions

After mtDNA release, excessive activation of cGAS-STING and subsequent neuroinflammation inevitably lead to neuronal death and loss. Although the role of the mtDNA-cGAS-STING pathway in the CNS has only been partially revealed in recent years, its potential as an emerging target for AD treatment has gradually become apparent, and its significance and prospective utility cannot be ignored. Therefore, besides alleviating and inhibiting the abnormal release of mtDNA or other dsDNA caused by mitochondrial stress and autophagy imbalance

[233], blocking the transmission of cGAS-STING signaling and the activation of its downstream inflammatory signals may represent a feasible approach for AD therapy [218].

Currently, a large body of preclinical research suggests that regulating the cGAS-STING is a promising intervention strategy (Table 3) (Fig. 5). Drugs targeting this pathway that have shown beneficial effects in AD animal or cellular models including H-151, RU.521, and C-176. For instance, H-151, inhibiting the palmitoylation of STING, and RU.521, targeting the catalytic site of cGAS, both significantly alleviated Aβ pathology in 5xFAD mice [145]; C-176 is an irreversible STING inhibitor that covalently binds to the Cys91 site of STING [234], significantly preventing neuroinflammation in microglia treated with $A\beta_{25-35}$, and showing even more pronounced effects with combined treatment with RU.521 [176]. In addition, certain drugs, such as NR and its metabolite NAD^+, the endogenous hormone melatonin, and the antibiotic dapsone [167, 171, 174, 175], all can non-specifically modulate this pathway to alleviate AD pathology. Although no drugs targeting this pathway have yet been approved for AD treatment, these studies provide valuable insights for the development of therapeutic drugs for AD in the future.

Despite significant progress in the research on cGAS-STING and its related modulators, there are still some issues that require clarification. Firstly, the cGAS and STING proteins are widely expressed in various tissues and cells, which may lead to significant adverse reactions when cGAS and STING modulators are used. Thus, when developing drugs targeting this pathway, it would be necessary to chemically optimize them to enhance target selectivity and deliver them selectively to the CNS, minimizing adverse reactions caused by their effects on the immune system throughout the body as much as possible. Additionally, owing to the functional diversity of cGAS and STING, and the complexity of the immune surveillance network [266, 267], complete inhibition of cGAS-STING signaling may not be a feasible approach. Specifically, prolonged inhibition of this pathway may be detrimental to the treatment of diseases requiring acute and beneficial initial neuroinflammatory responses, including stroke, spinal cord injury, and traumatic brain injury [268], although it may have relatively beneficial effects on chronic neurodegenerative diseases. At the same time, STING inhibitors may lead to excessive suppression of the body's immune system, thus impairing the immune surveillance of tumor cells to increase the risk of tumor occurrence [269], and weakening antiviral and antibacterial responses that could result in severe infections [189]. It is also essential to identify the balance point for the regulation of this pathway to ensure the maximum alleviation of AD pathology while avoiding other adverse reactions.

Secondly, in studies related to AD treatment, the expression of cGAS and STING has been reported in multiple types of neural cells [103, 117]. However, whether this pathway mediates diverse pathophysiological responses in different cell types still remains unclear. Additionally, there is as yet no consensus regarding the cell types in the brain expressing cGAS and STING and their expression levels in different cell types; the intracellular localization of cGAS has not been fully elucidated as well [270]. Thus, necessitating further research to explore their cellular distribution to provide compelling evidence for more precise targeted therapy.

Furthermore, a comprehensive consideration of other influencing factors to improve drug treatment efficacy is equally important. In addition to cGAS, other DNA sensors, such as IFN-γ inducible protein 16 (IFI16) and DEAD-box helicase 41 (DDX41), have been found to mediate downstream signaling through STING and appear to complement cGAS in pathogen detection under certain circumstances [17, 271]. Among them, DDX41 modulates cGAS activation by regulating the homeostasis of dsDNA and ssDNA [272]. However, the mechanisms of interaction among these DNA sensors remain largely unclear. Simultaneous interference with these pathways could potentially impair immune surveillance and increase susceptibility to certain diseases. Another issue that requires attention is that existing research on this pathway is mostly based on animal or cell models, and there may be species differences in cGAS and STING [268], which could lead to poor clinical outcomes. In addition, drugs must be transported from the periphery to the CNS through the blood–brain barrier (BBB), increasing BBB permeability and realizing precise targeting therapy also needs to be given priority. However, current studies on these drugs primarily focus on their anti-inflammatory effects and are limited to peripheral administration in animal or in cell models, with insufficient research on their ability to cross the BBB, specific distribution, and metabolic processes within the CNS. Moreover, optimizing drug delivery systems, such as nanoparticle-based carriers, carrier/receptor-mediated endocytosis, and exosome-mediated drug delivery [273–276], may offer breakthroughs in targeting the cGAS-STING pathway for AD treatment.

Conclusion

As research in the field has continued to advance, the mechanisms of mtDNA release and the specific role of the cGAS-STING pathway in AD are constantly being updated. Recent studies have revealed that mtDNA release and the activation of this pathway are

Table 3 The inhibitors targeting the cGAS-STING pathway

Targets	Agent	Mechanism	Pharmacological effect	References
cGAS Inhibitors	A151	Competes with DNA	Inhibits IFN-I production; attenuates brain inflammatory burden	[235, 236]
	Suramin	Displaces dsDNA from cGAS	Reduces IFN-I production	[237]
	AMDs (Hydroxychloroquine, Quinacrine, Chloroquine)	Disrupts the binding of dsDNA with cGAS	Reduces IFN-β production	[238, 239]
	X6	Disrupts the binding of dsDNA with cGAS	Reduces ISG expression and cGAMP production	[239]
	XQ2B	Targets the interface between cGAS and dsDNA and phase separation	Suppresses the elevated levels of type I interferon and proinflammatory cytokines	[240]
	CU.32, CU.76	Binds to the zinc-binding site of cGAS	Reduces IFN-β production	[241]
	4-sulfonic calix [6] arene	Influences both the dsDNA-binding site on cGAS and the 2′,3′-cGAMP	Dose-dependent inhibition in poly dA:dT-induced IFN-β release	[242]
	RU.521	Occupies the catalytic site of cGAS; reduce its affinity for ATP and GTP	Suppresses IFN- I production	[243]
	PF-06928215	Has high affinity for the catalytic site	Exhibits no inhibitory potency against dsDNA-induced IFN-β expression in cellular cGAS assays	[244]
	G140, G150	Inhibits the catalytic activity	Inhibits dsDNA-triggered interferon expression	[245]
	Compound S3	Inhibits the catalytic activity	-	[246]
	Compound 25	Occupies the catalytic site of cGAS	Dramatically suppresses the dsDNA-induced phosphorylation of the downstream STING/TBK1/IRF3 signaling and the mRNA expression of the downstream ISGs	[247, 248]
	EGCG	Disrupts cGAS activation by inhibiting of G3BP1	Inhibits self DNA-induced autoinflammatory responses and ISG expression	[249]
	aspirin	Inhibits cGAS by enforcing its acetylation	Suppresses self-DNA-induced autoimmunity in AGS patient cells and in an AGS mouse model	[194]
	FTO	Decreases cGAS mRNA stability by inhibition of m6A modification	Significantly alleviated brain injury and microglia-mediated inflammatory response	[250]
	Leptomycin B	Blocks the nuclear export of cGAS	Inhibits the expression of IFN-β and ISG mRNA	[251]
	Entinostat (MS275)	Suppresses cGAS transcription by inhibiting HDAC3	Reduces IFN-β production	[109]
	Trichostatin A (TSA)	Suppresses cGAS transcription by inhibiting HDAC3	Reduces IFN-β production	[109]
	Activin A	Inhibits cGAS-STING-mediated autophagy by the PI3K-PKB pathway	Alleviates neuronal injury	[252]
	Perillaldehyde	Inhibits cGAS activity through unknown mechanism	Reduction in type-I IFN- mediated inflammation in a mouse model of Aicardi-Goutières syndrome (AGS)	[253]
	TDI-6570	-	Suppresses IFN- I production	[103]
STING Inhibitors	Astin C	Inhibits STING by targeting its C-terminal activation pocket	Inhibits cytosolic DNA-trigged gene expression	[254]
	Compound 18	Inhibits STING by competing with cGAMP	Functional inhibition of STING-mediated cytokine release	[255]
	SN-011	Suppresses STING activation by blocking CDN binding pocket	Inhibits interferon and inflammatory cytokine induction induced by 2′3′-cGAMP	[256]
	C-176, C-178	Inhibits the palmitoylation of STING	Strongly reduced STING-mediated IFNβ reporter activity	[234]
	C-170, C-171, H-151	Inhibits the palmitoylation of STING	Abrogation of type I IFN responses, reduction of TBK1 phosphorylation and systemic cytokine responses	[234]

Table 3 (continued)

Targets	Agent	Mechanism	Pharmacological effect	References
	NO2-FAs	Blocks STING Palmitoylation	Inhibit Release of Type I IFN	[257]
	2-bromopalmitate (2-BP)	Inhibits the palmitoylation of STING	Abolishes the type I interferon response	[258]
	BPK-21, BPK-25	Inhibits the palmitoylation of STING	-	[259]
	CCCP	Inhibits phosphorylation of STING and the interaction between STING and TBK-1	Inhibits STING-mediated IFN-β production	[260]
	4-octyl itaconate (4OI)	Inhibits phosphorylation of STING by alkylating its cysteine sites 65, 71, 88	Represses type I IFN production	[261]
	ISD017	Blocks the essential trafficking of STING from the ER to Golgi	Inhibits the expression of IFN-I and blocks pathological cytokine responses	[262]
	4-HNE	Inhibits STING translocation from the ER to the Golgi	-	[263]
	Palbociclib	Targets Y167 of STING to block its dimerization	Alleviates autoinflammation	[264]
	SP 23	Modulates STING-degrading activities	Reduces proinflammatory cytokines and inhibited the expression of p-TBK1	[265]

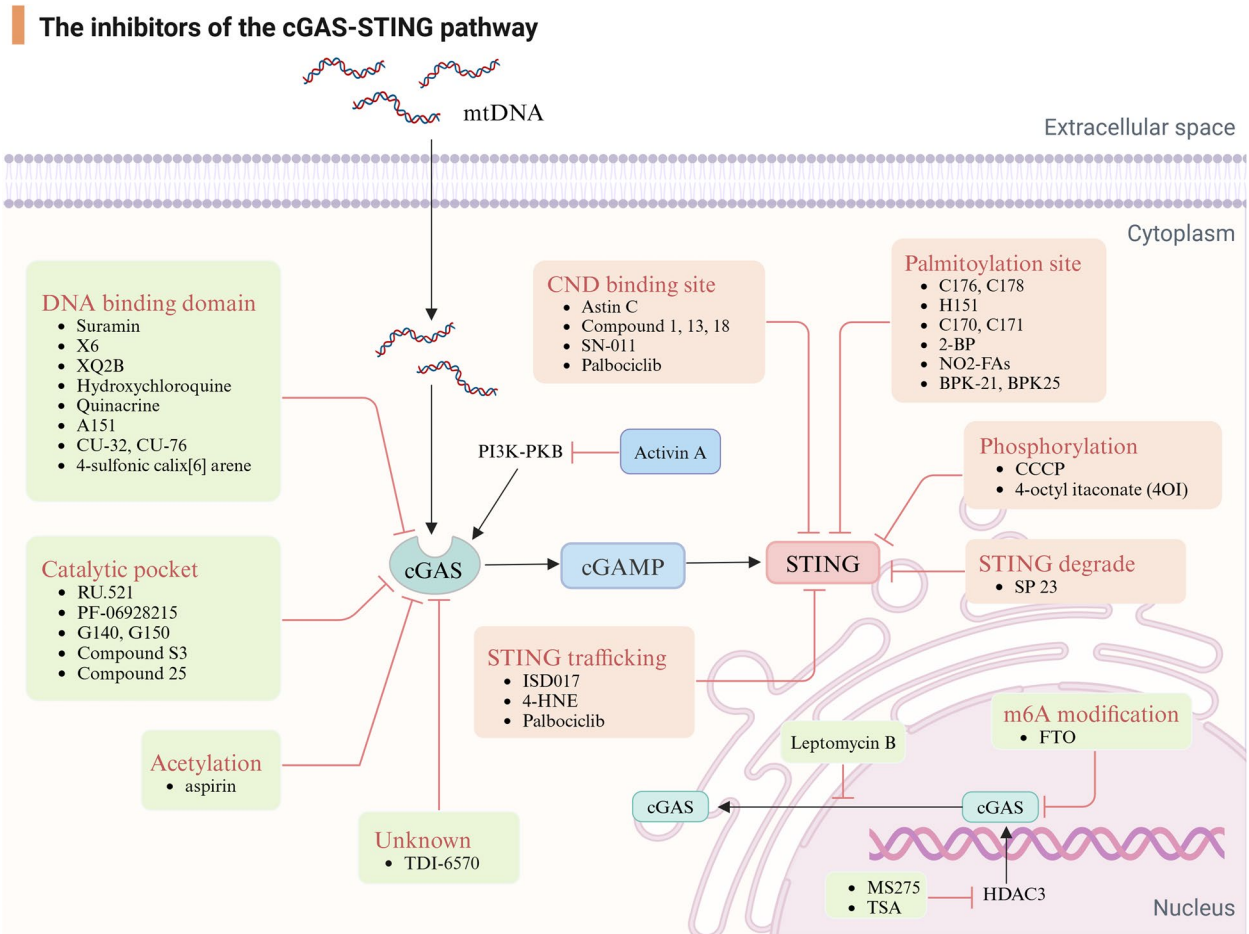

Fig. 5 Overview of the inhibitors targeting the cGAS-STING signal pathway

interconnected events that collectively drive AD progression. Due to the extensive spectrum of pathogenic mechanisms formed by the interaction of this pathway with AD pathological processes, including neuroinflammation, aging, and neurodegeneration, further exploration of their causal relationships is essential. Importantly, the development of modulators targeting this pathway may provide new therapeutic strategies for AD. In summary, a thorough investigation into the role of the mtDNA-cGAS-STING pathway in AD is crucial for understanding its pathogenesis, identifying new therapeutic targets, and providing more possibilities for alleviating symptoms and slowing disease progression in patients with AD.

Abbreviations

AD	Alzheimer's disease
NFT	Neurofibrillary tangles
DAMPs	Damage-associated molecular patterns
PRRs	Pattern recognition receptors
cGAS	Cyclic GMP-AMP synthase
mtDNA	Mitochondrial DNA
dsDNA	Double-stranded DNA
STING	Stimulator of interferon genes
CNS	Central nervous system
PD	Parkinson's disease
ALS	Amyotrophic lateral sclerosis
POCD	Postoperative cognitive dysfunction
TBE	Traumatic brain encephalopathy
miMOMP	Minority MOMP
VDAC	Voltage-dependent anion channel
OMM	Outer mitochondrial membrane
MOMP	Mitochondrial outer membrane permeabilization
EVs	Extracellular vesicles
NETs	Neutrophil extracellular traps
IFN	Interferon
IMM	Inner mitochondrial membrane
CICD	Caspase-independent cell death
MIMP	Mitochondrial inner membrane permeabilization
mt-dsRNA	Mitochondrial double-stranded RNA
ANT	Adenine nucleotide translocator
mPTP	Mitochondrial permeability transition pore
VRK2	Virus-related kinase 2
HK2	Hexokinase 2
ER	Endoplasmic reticulum
GSDMs	Gasdermins
IL-1β	Interleukin-1β
GSDMD	Gasdermin D
CSF	Cerebrospinal fluid
cf-mtDNA	Cell-free mtDNA
mtDNAcn	MtDNA copy numbers
TLR-9	Toll-like receptor-9
NLRP3	Nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR), and pyrin domain-containing protein 3
Mab21	Male abnormal gene family 21
2 '3'-cGAMP	2'3'-Cyclic GMP-AMP
GTP	Guanosine triphosphate
ATP	Adenosine triphosphate
CCT	C-terminal tail
TBK1	TANK-binding kinase 1
IRF3	Interferon regulatory factor 3
IFN-I	Type I interferons
ISGs	Interferon-stimulated genes
IKK	IκB kinase
NF-κb	Nuclear factor kappa-B
TNF-α	Tumor necrosis factor-alpha
IL-6	Interleukin-6
ERGIC	ER-Golgi intermediate compartment
LC3	Microtubule-associated protein 1 light chain 3
MEF2C	Myocyte enhancer factor 2c
TDP-43	Transactive response DNA binding protein of 43 kDa
GWAS	Genome-wide association analysis
APOE	Age and apolipoprotein E
TREM2	Triggering receptors expressed on myeloid cells 2
ABCA	ATP-binding cassette subfamily A
Aβ	β-Amyloid
TOM	Translocase of the outer membrane
DSBs	DNA double-strand breaks
APP/PS1	APPswe/PS1dE9
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1 alpha
TFAM	Mitochondrial transcription factor A
NEUROD6	Neurogenic differentiation factor-6
APP-CTF	Amyloid precursor protein-C-terminal fragment
SASP	Senescence-associated secretory phenotype
L1	LINE-1
IRM	Interferon-responsive microglia
DAM	Disease-associated microglia
MGnD	Neurodegenerative microglia
PQBP1	Polyglutamine-binding protein 1
IFI16	Interferon inducible protein 16
DDX41	DEAD-box helicase 41
BBB	Blood-brain barrier

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Authors' contributions
LJ and SQ contributed to the conception and the structure of the manuscript. The manuscript was drafted by SQ, and then commented upon and edited by all authors. All authors read and approved the final manuscript.

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