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cGAS-STING signaling in brain aging and neurodegeneration: molecular links and therapeutic perspectives

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Abstract

Aging is a major risk factor for neurodegenerative diseases, yet the underlying mechanisms linking aging to neurodegeneration remain incompletely understood. The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway plays a critical role in sensing mislocalized cytoplasmic DNA, triggering innate immune responses such as type I interferon (IFN-I) and NF-κB signaling, and promoting senescence-associated secretory phenotypes (SASP). In the aging central nervous system (CNS), cellular senescence is accompanied by mitochondrial DNA (mtDNA) leakage, nuclear DNA damage, and other changes that may aberrantly activate the cGAS-STING pathway. This activation drives neuroinflammation, potentially increasing susceptibility to neurodegenerative diseases or exacerbating pre-existing pathology. Conversely, neurodegenerative disease-related processes-such as pathological protein aggregation-can further stimulate cGAS-STING signaling, amplifying inflammatory cascades and accelerating cellular senescence. This review explores the molecular mechanisms linking cGAS-STING activation to neurodegeneration and discusses potential therapeutic strategies targeting this pathway.

Keywords Aging, Neuroinflammation, Microglia, Neurodegenerative diseases, cGAS-STING pathway

Introduction

Systemic, chronic, low-grade inflammation is a hallmark of aging [1, 2]. Even in the absence of overt infection, aged organisms develop a persistent inflammatory state, which contributes to tissue degeneration and increases susceptibility to age-related diseases. This condition, often termed "inflammaging," is a key risk factor for multiple pathologies, including hypertension, atherosclerosis, type 2 diabetes, cancer, and neurodegenerative disorders [3–5].

The sources of aging-related inflammation (inflammaging) are multifactorial. With aging, heightened oxidative stress generates excessive free radicals, leading to progressive accumulation of damaged cells, organelles, and harmful metabolites. These components are often recognized by the immune system as damage-associated molecular patterns (DAMPs), triggering chronic inflammatory responses [6]. Concurrently, age-related immune dysfunction impairs the clearance of senescent cells and cellular debris, resulting in their pathological accumulation. This creates a vicious cycle that perpetuates and amplifies senescence-associated inflammation [7].

At the cellular level, aging is characterized by the development of senescence-associated secretory phenotype

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(SASP) [8]. SASP represents a critical mechanism through which senescent cells influence their microenvironment, mediating both local and systemic biological effects. This complex secretory profile includes pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, etc.), chemokines (CCL2, CCL5, etc.), growth factors (TGFβ, etc.) and metalloproteinases (MMP1, etc.), as well as biologically active lipids, non-coding nucleic acids, etc [9]. Through SASP, senescent cells create a pro-inflammatory microenvironment that not only sustains chronic inflammation but also propagates the senescent phenotype to neighboring cells, establishing a self-reinforcing cycle of inflammation and cellular senescence [1]. While persistent DNA damage response (DDR) activation is recognized as a key driver of SASP [10], the precise molecular mechanisms governing SASP induction remain incompletely understood.

Neuroinflammation in neurodegenerative diseases

Neurodegenerative diseases are a group of disorders characterized by the progressive degeneration of the structure or function of neurons in the central nervous system (CNS) or peripheral nervous system (PNS), including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). Neuroinflammation is one of the common risk factors for these neurodegenerative diseases and a complex response of the CNS to certain stimuli, characterized by the activation of the innate immune system, elevated levels of pro-inflammatory cytokines, and enhanced microglial activation [11–13].The release of inflammatory mediators such as cytokines, histamine, and reactive oxygen species (ROS) by microglia, astrocytes, and immune cells is a core element in triggering neuroinflammation [14]. These mediators can, to some extent, modulate neurotransmitter release, receptor expression, and synaptic plasticity, contributing to the protection of the brain against pathogens. However, inappropriate or chronically expressed inflammatory mediators may induce neuronal oxidative stress, leading to synaptic loss, neuronal dysfunction, and even cell death, thereby increasing the risk of developing neurodegenerative diseases [15].Furthermore, neuroinflammation can compromise the integrity of the blood-brain barrier (BBB), allowing peripheral immune cells to infiltrate the brain. These cells release their own inflammatory mediators, thereby exacerbating the already elevated neuroinflammatory state. This breach may also permit the entry of pathogens, toxins, and metabolic waste into the CNS, complicating the damage caused by inflammation [16].

The aging brain is prone to induce neuroinflammation [17] because cells of the aging CNS, including astrocytes, microglia, and oligodendrocyte progenitors, accumulate during the course of normal aging and neurodegenerative disorders and produce a range of factors that exhibit features of SASP. Their SASP are thought to be associated with age-related tissue inflammation and to promote neurodegeneration [18, 19], and different neurodegenerative disorders, although exhibiting different pathologic features, have been shown to have a neuroinflammatory contribution to the pathologic process. AD is characterized by the deposition of amyloid plaques formed by β-amyloid (Aβ) and the accumulation of neurofibrillary tangles composed of hyperphosphorylated Tau protein. Its incidence and severity are highly age-dependent [20]. Particularly in the early stages of AD, patients' brains exhibit significant chronic neuroinflammatory responses, and this inflammation can exacerbate Aβ deposition and tau protein hyperphosphorylation [21, 22].

Specifically, PD is characterized by progressive degeneration of dopaminergic neurons in the substantia nigra of the brain and the accumulation of Lewy bodies, leading to motor deficits, pro-inflammatory phenotypes, and neurodegeneration. In PD, inflammation can promote the aggregation of α-synuclein (α-syn), resulting in the formation of Lewy bodies [13, 23]. ALS is a fatal neurodegenerative disorder that selectively attacks upper and lower motor neurons, causing progressive paralysis and muscle atrophy. Neuroinflammation is also involved in the occurrence and progression of ALS [24]. Activated and proliferating microglia, infiltration of T lymphocytes, and the production of various inflammatory factors can be found in the affected tissues, such as the brainstem and spinal cord, of ALS patients [25]. HD is an inherited neurodegenerative disorder in which patients exhibit loss of motor control, cognitive impairment, and significant changes in mood and mental state. Individuals with HD display significant inflammation in the striatum, basal ganglia, and cortex, indicating that neuroglia-mediated neuroinflammation contributes to cell death [26].

The cGAS-STING pathway in neuroinflammation and neurodegenerative diseases

Pattern recognition receptors (PRRs) are a class of recognition molecules primarily expressed on the surface of innate immune cells and distributed non-clonally. They can detect invading pathogens or viral components and respond to local damage and damage-associated molecular patterns (DAMPs) [27]. Among these, the cyclic guanosine monophosphate-adenylate synthase (cGAS), a key sensor for cytosolic DNA, is a classic PRR primarily localized in the cytoplasm, capable of recognizing DNA in the cytoplasm. It regulates the expression of downstream cytokines, such as type I interferons (IFNs), thereby triggering various inflammatory responses [28, 29]. cGAS directly binds to the double-stranded DNA (dsDNA) and triggers a conformational change and activating its enzymatic activity. Activated cGAS further utilizes GTP and

ATP as substrates to catalyze the synthesis of the second messenger cyclic GMP-AMP (cGAMP) to facilitate the downstream pathways [30, 31]. cGAS can recognize pathogen double-stranded DNA (dsDNA) regardless of its sequence or origin, thereby recognizing a variety of exogenous and endogenous dsDNA. This includes DNA leaked from the cell nucleus and mitochondria, DNA obtained from the extracellular microenvironment, dsDNA viruses, retroviruses, and pathogen DNA from certain intracellular bacteria and parasitic protozoa [32–34].

Upon activation, cGAS initiates a series of downstream signaling pathways. Among these, the cyclic guanosine monophosphate-adenylate synthase (cGAS)-stimulin-like receptor-like protein (STING) pathway has recently been identified as linking nucleic acid sensing to immune responses, representing a core risk sensing pathway in the innate immune system [35]. Stimulator of interferon genes (STING) is an endoplasmic reticulum (ER) membrane protein encoded by transmembrane protein 173 (TMEM173). The upstream action of cyclic GMP-AMP synthase (cGAS) is the primary pathway inducing STING activation [36]. In the cGAS-STING pathway, STING and cGAS exhibit critical synergistic effects: when recognizing and binding to DNA, cGAS synthesizes the second messenger 2',3'-cGAMP. This messenger binds to STING on the ER, inducing a conformational change in STING. Subsequently, STING is transported from the ER to the ER-Golgi intermediate compartment (ERGIC) and the Golgi apparatus via a mechanism dependent on the cytoplasmic envelope protein complex II (COP-II). At these locations, STING recruits TANK-binding kinase 1 (TBK1) to form a signaling complex, promoting TBK1 autophosphorylation [37]. TBK1 then phosphorylates STING, providing a binding site for interferon regulatory factor 3 (IRF3) and inducing its phosphorylation. Phosphorylated IRF3 is transported to the nucleus, thereby inducing the transcription of IRF3 target genes and the release of type I interferon (IFN-I) [38].

In the Golgi apparatus, activated STING can also recruit and induce the phosphorylation of IκB kinase (IKK) via TBK1. This subsequently activates the NF-κB signaling pathway downstream of IKK, initiating the transcription of numerous immune-related genes and anti-apoptotic genes [28, 39].Upon translocation to the ERGIC, STING utilizes the ERGIC as a membrane source for microtubule-associated protein 1 A/1B-light chain 3 (LC3) lipidation, leading to autophagosome formation. These autophagosomes are responsible for removing damaged STING and cGAS molecules [34]. Additionally, the STING protein can specifically bind to COPI vesicles via the bridging protein Surfeit locus protein 4 (SURF4), ultimately being delivered to the autolysosomal system for catabolism. This process achieves timely termination of STING signaling [40].Notably, although the importance of the mechanisms described above in mediating inflammatory regulation is well-established, accumulating evidence indicates that the functional diversity of downstream effectors in the cGAS-STING pathway far exceeds current understanding. Depending on the specific cell population or disease context, cGAS-STING activation can trigger markedly distinct biological effects [23, 28, 41].

In recent years, aberrant activation of the cGAS-STING pathway has been reported to be involved in the pathogenesis of numerous neurodegenerative and inflammatory diseases [42, 43]. Mounting evidence indicates that the cGAS-STING pathway serves as a key driver of chronic neuroinflammation and cognitive decline during the aging process [44, 45]. Prolonged and uncontrolled activation of the cGAS-STING pathway drives age-related neurological disease progression through neuroinflammation, amplifying the pathological damage caused by a variety of neurodegenerative disorders, in which microglia play a particularly critical role. In the CNS, microglia maintain brain health through trophic support, removal of histiocyte debris, and participation in immune defense, and are the brain-resident immune cell type with the highest expression of cGAS-STING and the most direct functional roles [46]. cGAS-STING pathway is closely related to microglia mediated neuroinflammation and abnormal activation of microglia has been reported in a variety of neurodegenerative diseases, including AD and PD.

Research has shown that abnormal aggregation of microglia and a reduction in hippocampal neurons are observed in the brain tissue of aged mice, while inhibition of STING gene expression significantly alleviates inflammatory responses and neurodegeneration in the central nervous system of aged individuals [47]. As the immune sentinels of the central nervous system, microglia are extremely sensitive to environmental changes. When the stability of the genome is disrupted due to aging, this imbalance in the central nervous system microenvironment can lead to the persistent activation of microglia and the continuation of neuroinflammation. In the context of aging-related gene imbalance, imbalance in the central nervous system microenvironment may continuously activate microglia, causing the neuroinflammatory process to become permanent [48]. In addition, abnormal activation of the cGAS-STING pathway in the central nervous system of aging mice was significantly correlated with functional decline and cognitive deficits in the organism [49]. Significantly higher levels of cGAMP were detected in brain tissue lysates from aged mice compared to young controls, suggesting possible dysregulation of cGAS activity during aging [47]. Xie et al. observed specific binding events of cGAS to dsDNA

in aged brain tissue, accompanied by excessive cGAMP production and a synchronous elevation in levels of IFN-I-related inflammatory markers within hippocampal tissue and microglia. This provides evidence for dysregulation of the cGAS-STING pathway during aging [50]. Furthermore, Zhang and colleagues identified characteristic alterations indicative of enhanced cGAS signaling pathway activity in the frontal cortex of aged non-human primates. Concurrently, they detected significant upregulation of NF-κB levels and downstream pro-inflammatory cytokine genes in this region. This phenomenon was also validated in human aged brain tissue, indicating that hyperactivation of the cGAS signaling pathway may represent a significant hallmark of physiological aging in mammals [51].

Intriguingly, cGAMP can also be transported intercellularly and might function as an important immunotransmitter to the propagating senescence program in neighboring cells [52]. Brain metastatic cancer cells establish Cx43 gap junctions with astrocytes via the primary cadherin PCDH7 and use this to transfer cGAMP into astrocytes, activating STING and upregulating downstream inflammatory factors such as IFN-α and TNF. These factors feedback to cancer cells via paracrine signaling, activating STAT1 and NF-κB pathways, thereby promoting tumor growth and chemotherapy resistance [53]. Whereas, ATP binding cassette sub-family C member 1 (ABCC1)-mediated cGAMP export limited cell-intrinsic activation of STING and ameliorated STING-dependent autoimmune disease in various cell types such as human foreskin fibroblasts (HFF) and bone-marrow-derived macrophages (BMM) [54]. More recently, it has been verified that the transfer of cGAMP from neuron to microglia via canonical volume-regulated anion channels (VRACs) triggers type I interferon response and amplifies neuroinflammation after subarachnoid hemorrhage, and the VRACs inhibitor endovion attenuates microglia activation and thereby reduced neuronal apoptosis [52].

In addition to mediating age-related non-specific neuroinflammation, the cGAS-STING pathway exhibits its specific mechanisms in different neurodegenerative diseases(Fig.1). This suggests that the function of the cGAS-STING pathway is not limited to serving as a simple initiator of inflammatory responses but rather as a key regulatory hub integrating pathological proteins, DNA damage patterns, and risk genes. The influence of genetic factors on the development of neurodegenerative diseases has been well established, and the cGAS-STING pathway may be abnormally activated under the influence of these genetic factors. The lipid transport protein APOE4, expressed on astrocytes and microglia, is associated with early-onset AD, higher levels of Aβ and tau toxicity, and increased microglia inflammation, making it the strongest genetic risk factor for the development of late-onset AD [55]. Additionally, TREM family proteins are part of the neuroinflammatory cascade in AD, and when activated by factors such as STING, NF-κB regulates the expression of TREM1 and TREM2 [56]. The e4 allele of APOE and the R47H point mutation of the TREM2 receptor are believed to potentially lead to an increase in BAX-mediated mtDNA leakage and DNA damage by altering mitochondrial membrane permeability, and the cGAS-STING pathway may be activated on this basis [57]. Additionally, the R47H mutation has been shown to exacerbate microglial inflammation, impair ligand binding, and weaken the ability of microglia to surround and phagocytose Aβ plaques [58]. However, the direct mechanisms linking these AD-associated genetic variants to cGAS-STING pathway activation requires further experimental clarification. In Parkinson's disease (PD), defects in the genes PINK1 and parkin related to PD have been reported to activate the cGAS-STING pathway, leading to the characteristic pathological changes of PD. The mechanism may involve the small interfering RNA of PINK1 promoting the release of mtDNA by down-regulating mitochondrial autophagy, as well as the mitochondrial-derived dam-related molecular patterns (mtDAMPs) triggered by the absence of parkin [59]. Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene represent the most common genetic cause of hereditary Parkinson's disease (PD) [60]. LRRK2 indirectly suppresses the type I interferon (IFN-I) response by limiting NRF2 expression in microglia [61]. LRRK2 mutations enhance oxidative stress levels, leading to mitochondrial DNA (mtDNA) leakage and chronic activation of the cGAS-STING signaling pathway [62].Regarding amyotrophic lateral sclerosis (ALS), its pathology is associated with either a gain-of-function from dipeptide repeat proteins encoded by hexanucleotide repeat expansions or a loss-of-function due to reduced expression of C9ORF72 [63]. Deletion of the C9ORF72 gene can impair STING degradation and cause excessive IFN-I expression in myeloid cells and microglia [64, 65].

Abnormal aggregation of pathological proteins is an important feature of neurodegenerative diseases, such as Aβ in AD, α-syn in PD, TDP-43 in ALS, and mHTT in HD [66]. These pathological protein deposits are significantly associated with aberrant activation of the cGAS-STING pathway: in AD, IFITM3z acts as a positive regulator of γ-secretase to promote the accumulation of Aβ, the cleavage product of amyloid precursor protein (APP) [67], whereas cGAMP and IFN-I in neurons and astrocytes are able to induce the up-regulation of IFITM3. Therefore, the activation of the chronic cGAS-STING pathway may promote the accumulation of Aβ by up-regulating IFITM3 [68, 69]. These pathological responses were partially reversed by blocking the

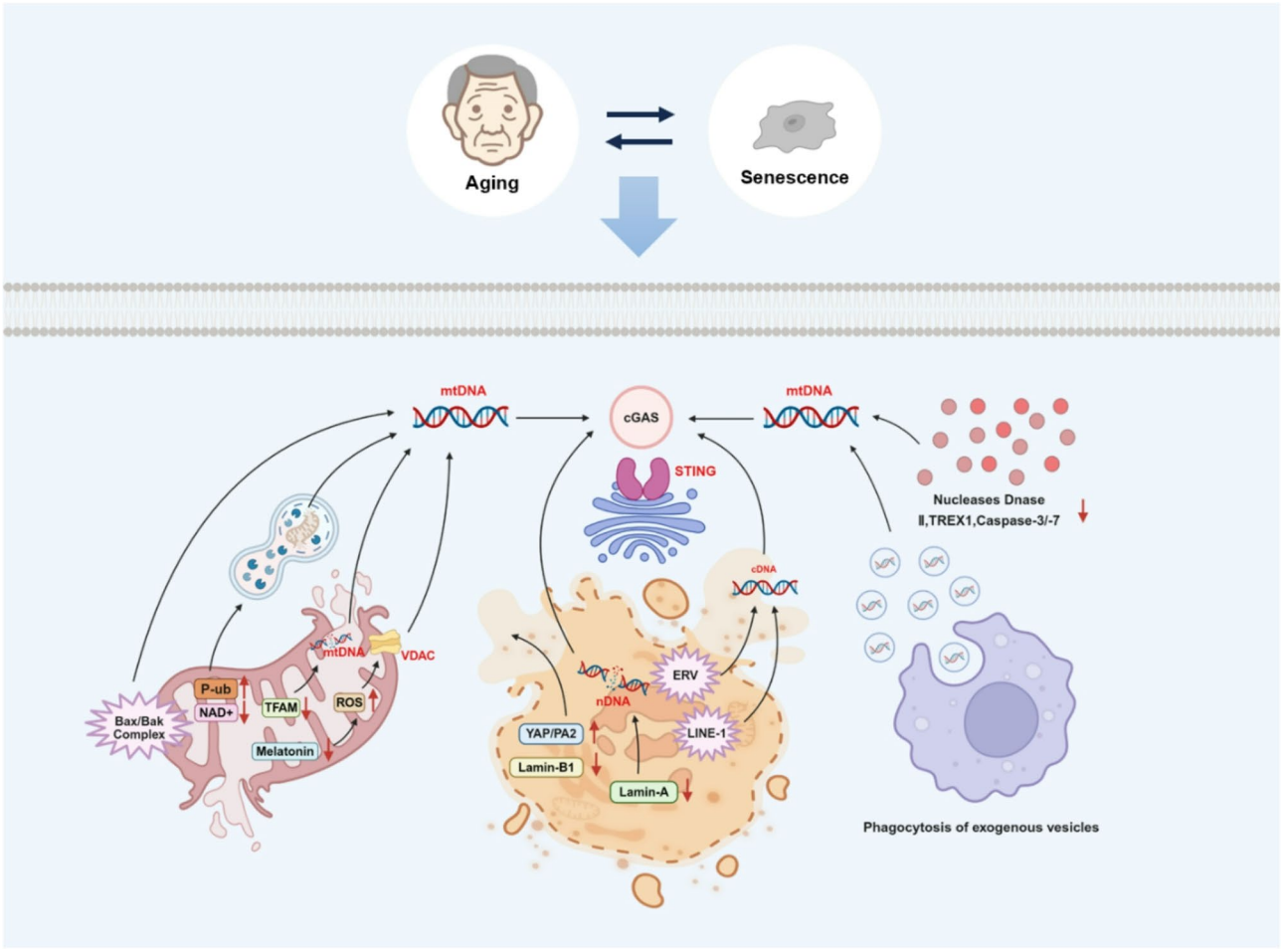

Fig. 1 Aging-related factors activate the cGAS-STING pathway in the CNS. Aging increases DNA accumulation in the cytosol and activates the cGAS-STING pathway through multiple mechanisms. ROS accumulation leads to mtDNA release into the cytosol through damaged mitochondrial membranes, a process exacerbated by impaired mitophagy during aging. Nuclear membrane stability is compromised due to factors such as reduced lamin proteins, causing leakage of unstable nuclear DNA. Cytosolic DNA levels are further increased by DNA fragments generated following the activation of retrotransposons. The diminished function of DNases responsible for clearing cytosolic DNA hinders its effective removal. Additionally, microglia can take up exogenous DNA-containing vesicles into the cytosol

cGAS-STING pathway, e.g., cGAS inactivation prevented the toxic effects of Tau proteins, and STING inhibition reduced Aβ aggregation, Tau phosphorylation, and aberrant synaptic loss [70, 71]. In a PD model, sustained activation of the STING signaling pathway was found to induce dopaminergic neuronal degeneration and promote abnormal aggregation of pathological α-syn [72]. As a downstream effector molecule of the cGAS-STING pathway, LCN2 is involved in regulating astrocyte senescence. Jiang et al. 's research shows that STING upregulates LCN2 expression by inhibiting the transcription factor YY1 (which negatively regulates LCN2 expression), which may promote astrocyte senescence and the progression of Parkinson's disease (PD) [73]. cTBK1 mutations have been identified as the genetic cause of nonsense, shifted-code, missense, and deletion mutations in familial ALS, and the GAS-STING pathway downstream of the dysregulation of TBK1 contributes to the development of pathogenic aggregates and neuroinflammation in ALS [74].

The pathological changes of neurodegenerative diseases may further activate the cGAS-STING pathway. Some experiments based on AD models have observed that tangles of beta-amyloid (Aβ) and tau proteins can induce mitochondrial oxidative stress, leading to the release of mitochondrial DNA (mtDNA) into the cytoplasm of microglia and thereby activating cGAS [68, 71]. In microglia, polyglutamine binding protein 1 (PQBP1) may senses exogenous tau protein through direct interaction, triggering an innate immune response via activation of the cGAS-STING pathway [75]. Impairment of autophagy function, another hallmark of AD, can be helpful to the accumulation of damaged mtDNA in the cytosol [76]. Scopa et al. observed that upregulation of the AP-1 subunit, c-Jun, in hippocampal precursor cells (hpNPCs) and CA3 neurons derived from AD

patients activated retrotransposons (RTEs), promoting the abnormal accumulation of RNA-DNA hybrids in the cytosol. This subsequently activated the cGAS-STING pathway, inducing neuroinflammation and neuronal apoptosis [77]. In PD, α-syn can induce DNA double-strand breaks in microglia. It can also increase STING expression and enhance canonical STING activation, leading to STING-dependent neuroinflammation and dopaminergic neurodegeneration. Studies have observed significant upregulation of STING protein in the substantia nigra pars compacta of PD patients, correlating with pathological α-syn accumulation, further validating this mechanism [64, 78]. Furthermore, lysosomal leakage in dopaminergic neurons has also been reported to activate the cGAS-STING pathway [70]. In some cases of amyotrophic lateral sclerosis (ALS), TDP-43 has been reported to invade mitochondria and trigger mtDNA release through permeability conversion pores, activating cGAS and its downstream signal transduction [79]. Cytoplasmic aggregates of wild-type superoxide dismutase 1 (SOD1) are commonly present in ALS patients. Some studies suggest that misfolded SOD1 protein induces mitochondrial dysfunction and promotes the leakage of mtDNA and RNA-DNA heterozygotes into the cytoplasm through a non-MPTP-dependent mechanism, thereby activating the cGAS-STING signaling axis [80]. In HD, misfolded mutant mHTT can increase the level of oxidative stress in the cortex and striatum of mice, leading to mtDNA leakage. Therefore, the activation of cGAS may be induced by DNA damage caused by mutant HTT protein (mHTT) in HD [81]. Notably, activation of the cGAS-STING pathway by pathological protein deposition may occur before the onset of classic neurodegenerative disease pathology. For instance, in the AD brain, the accumulation of plaques and tangles precedes the appearance of typical clinical symptoms by decades, and the detrimental effects of pathological protein accumulation gradually worsen with age [82]. Therefore, similar to the aforementioned age-related changes, pathological proteins are also regarded to a certain extent as important aging-related activators upstream of the cGAS-STING pathway.

Although many of the above-mentioned mechanisms have not been fully confirmed in systematic model studies or clinical cases, current research still reflects a bidirectional relationship between the occurrence of neurodegenerative diseases and the activation of the cGAS-STING pathway: On one hand, cGAS-STING pathway activation accelerates neurodegenerative pathologies by triggering neuroinflammation and promoting the deposition of pathological proteins. On the other hand, the deposition of pathological proteins associated with neurodegenerative diseases can further activate the cGAS-STING pathway, creating a vicious cycle.

Aging-related factors and the activation of the cGAS-STING pathway in the CNS

mtDNA

Mitochondrial damage is a traditional hallmark of aging [83, 84]. Due to the lack of an intact damage repair mechanism, mtDNA is more fragile than nuclear DNA (Fig.2). During mitochondrial injury or dysfunction, disruption of its inner membrane integrity leads to the opening of the mitochondrial permeability transition pore or changes in membrane permeability, prompting the release of free mtDNA into the cytoplasm in response to the imbalance of the membrane potential and the swelling of the mitochondrial matrix [85]. These spilled mtDNAs are specifically recognized by the cGAS as a danger-associated molecular pattern and bind to the mitochondrial matrix, activates the cGAS to trigger inflammation, and this occurrence becomes more prevalent with age [86, 87]. A recent study found that brain cells from 20-month-old WT mice exhibited higher levels of mtDNA compared to 3-month-old WT mice further demonstrated that cytoplasmic mtDNA accumulates in aging brain cells [50].

Excessive reactive oxygen species (ROS) production is the main cause of mtDNA damage [88, 89]. Oxidative stress theoretical model suggests that accumulation of ROS triggers pathological processes such as lipid peroxidation, abnormal energy metabolism, genetic material damage, and inflammatory responses, ultimately triggering neuronal degeneration with concomitant cognitive impairment [90]. Gradual accumulation of ROS in brain tissues during aging, may be related to the decline of endogenous antioxidant system functions [91]. Among them, melatonin, a free radical scavenger synthesized by neuronal mitochondria, shows a decreasing trend in concentration with age. This molecule maintains mitochondrial membrane permeability by neutralizing reactive oxygen species regulating pore stability and membrane potential homeostasis, and when insufficient, it exacerbates mitochondrial oxidative damage, which contributes to the aberrant release of mtDNA into the cytoplasm [92]. Due to the weak repair capacity of mtDNA itself and its spatial localization adjacent to mitochondrial ROS generation sites, mtDNA is more susceptible to oxidative stress damage generated by the electron transport chain (ETC) [93]. Studies targeting this mechanism have shown that significantly elevated levels of oxidative stress can drive mtDNA leakage into the cytoplasm or extracellular space. Corresponding molecular mechanism studies revealed that mitochondrial stress may mediate the exocytosis of mtDNA by activating voltage-dependent anion channels (VDACs) in the outer membrane, which promotes the oligomerization of channel proteins and the formation of transmembrane pore structures [94]. Pro-inflammatory mediators released by damaged

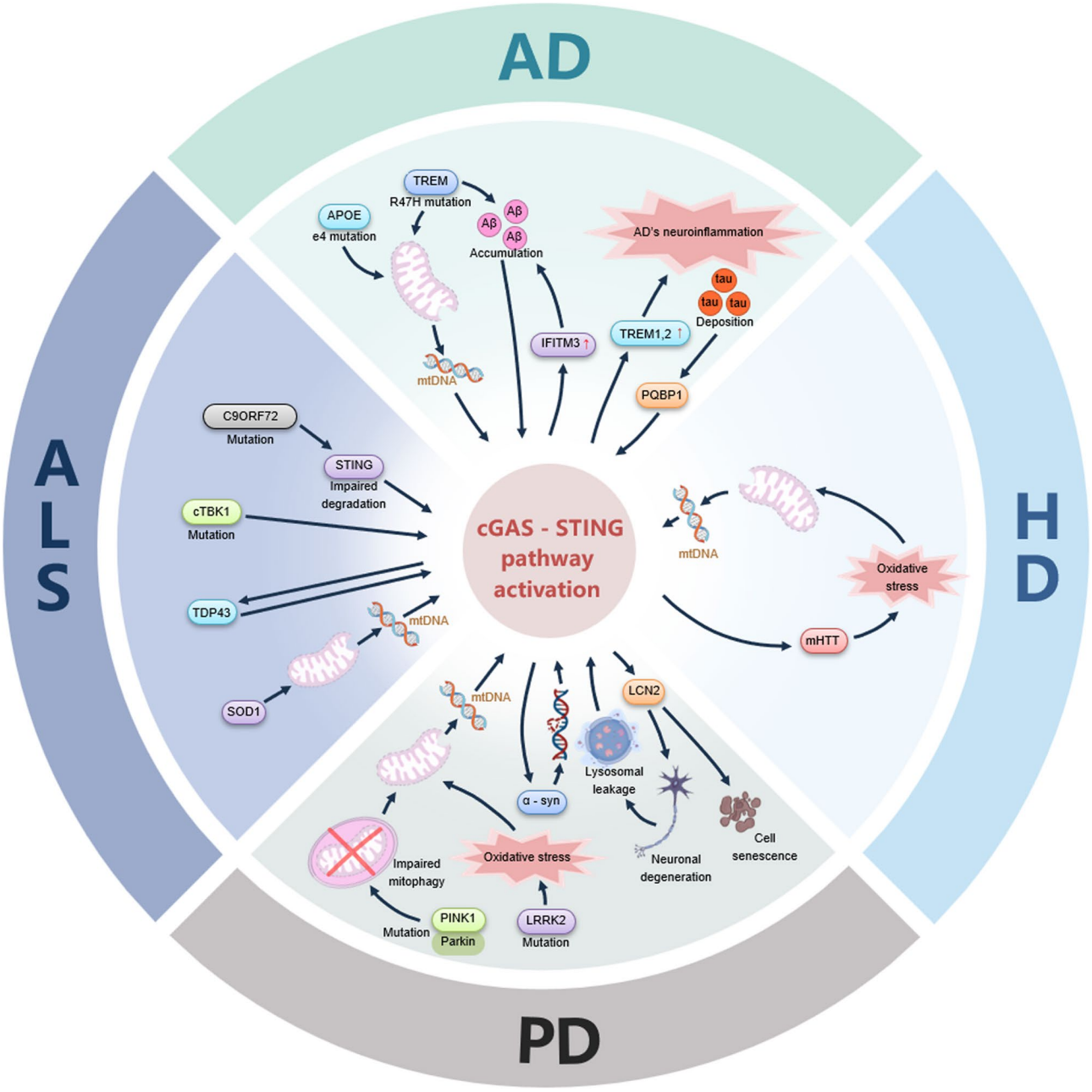

Fig. 2 Characteristic cGAS-STING pathways in different neurodegenerative diseases. In Alzheimer's disease, mutations in APOE4 and TREM2 lead to mtDNA leakage by impairing mitochondrial membrane permeability, activating the cGAS-STING pathway and promoting Aβ accumulation. Aβ and tau tangles can further activate this pathway. In Parkinson's disease, defects in the PINK1, Parkin, and LRRK2 genes cause mtDNA release, activating the cGAS-STING pathway and promoting abnormal α-syn aggregation. α-syn aggregates themselves can induce DNA damage and increase cytosolic DNA accumulation. In ALS, loss of function in the C9ORF72 gene impairs STING degradation; pathogenic TDP-43 and misfolded SOD1 proteins induce mitochondrial dysfunction that promotes leakage of molecules including mtDNA. In Huntington's disease, mutant mHTT elevates oxidative stress levels, triggers mtDNA leakage, and ultimately activates the cGAS-STING pathway

mitochondria and ROS can synergistically activate the neuroinflammatory response, and this pathologic inflammatory microenvironment causes further damage to mitochondria, forming a self-reinforcing malignant feedback loop [95].

Mitochondrial Transcription Factor A (TFAM) expression levels show a progressive decline in brain tissue aging processes [96]. TFAM forms nuclear-like structures by organizing mitochondrial DNA (mtDNA) and regulates their distribution and stability. Its absence may trigger the disassembly of the mitochondrial genome and

induce a mitochondrial stress response, leading to the escape of mtDNA from damaged mitochondria into the cytoplasm. Some studies suggest that such cytoplasmic mtDNA may further activate the cGAS-STING signaling axis and promote the transcriptional activation of downstream interferon-stimulated genes (ISGs). Although this mechanism has not been directly confirmed in neurodegenerative diseases, existing research still reflects a potential link between TFAM downregulation and neuroinflammation [97]. The continuous activation of pro-apoptotic signaling pathways during organismal aging leads to the accumulation of apoptosis-related molecules. When the apoptotic program is initiated, the BAX/BAK protein complex is activated and regulates changes in mitochondrial outer membrane permeability, at which time mtDNA fragments can be effluxed by means of the mitochondrial permeability transition pore (MPT) [98], and mtDNA free to the cytoplasm achieves the activation of the signaling pathway by specifically binding to cGAS. Mitochondrial outer membrane permeability (MOMP) is one of the central features of apoptosis and is manifested in senescent cells as a subcellular event that occurs in only a fraction of mitochondria, and this specific MOMP that triggers inflammation rather than programmed death has been defined as a minority MOMP (miMOMP). Studies have shown that in cellular senescence models, the miMOMP process depends on BAX/BAK-mediated membrane pore formation to promote mtDNA release, thereby increasing the level of free mtDNA in the cytoplasm and providing favorable conditions for cGAS activation. Animal experiments confirmed that the application of BAX inhibitor BAI1 to intervene in the aged mouse model could effectively alleviate the inflammatory response in the brain [99]. In addition, human endogenous retrovirus type K (HERVK), a repetitive genetic element closely associated with brain aging, showed a significantly high expression in brain tissues, especially in individuals over 60 years of age [100]. This retroviral element enhances cGAS-STING signaling through specific molecular mechanisms, which in turn induces senescence phenotypes and inflammatory responses in human cell lines and mouse models [31]. Notably, HERVK components generated in senescent cells can also diffuse to neighboring normal cells via the paracrine pathway, triggering premature aging in non-senescent cells [101].

The sources of mitochondrial DNA (mtDNA) that activate the cGAS-STING pathway in microglia not only include endogenous DNA released by mitochondria [102], but may also come from exogenous mtDNA-carrying vesicle structures taken up through the cytoplasmic pathway, such as neuron-derived exosomes, microvesicles and apoptotic vesicles [86]. The mtDNA vesicles in the peripheral circulation can breach the blood-brain barrier and are recognized and internalized by microglia in the brain. These exogenous mtDNA fragments are called circulating free mitochondrial DNA (ccf-mtDNA) [103], and their concentration accumulates significantly with age. Based on this, it may be hypothesized that the accumulation of ccf-mtDNA may also trigger abnormal activation of microglia, leading to their continuous release of neurotoxic inflammatory factors, thereby inducing a chronic neuroinflammatory state in the aging brain and possibly accelerating the pathological process of neurodegenerative diseases [104]. However, this hypothesis needs to be verified by more experimental results.

Nuclear DNA

In senescent cells, chromatin fragments may enter the cytoplasm via defective nuclear membranes and through a number of nuclear export processes such as chromatin budding and micronucleus formation, which in turn bind to cGAS and activate the cGAS-STING pathway [105]. In neuronal cells in the hippocampus of senescent mice and humans, due to decreased expression of laminin B1 (lamin-B1) [106], the mechanical stability of the nuclear membrane is generally impaired in senescent cells, thus allowing cGAS in the cytoplasm to be readily transferred across the damaged nuclear membrane to exposed chromatin DNA and activated. In premature aging diseases such as HGPS caused by truncation of lamin A, DNA replication stress triggered by lamin A deletion exacerbates genomic instability, and this intranuclear homeostatic imbalance ultimately triggers aberrant activation of cGAS-STING signaling (Fig. 1) [29].

Cytoplasmic reverse transcription transposon factors can be reactivated during somatic tissue senescence to activate the cGAS-STING pathway. Reverse transcriptional transposon activation marked by Long Interspersed Nuclear Element-1 Open Reading Frame 2 protein (LINE-1 ORF2p) accumulation was observed in the hippocampus of aged primates such as Crab-eating monkeys [107]. In contrast, another study reported that LINE-1 possesses reverse transcriptase activity to transcribe mRNA to cDNA in the cytoplasm, suggesting that increased LINE-1 transcription during senescence promotes cDNA accumulation in the cytoplasm and triggers cGAS-STING signaling [108]. Furthermore, Zhang et al. observed that during the aging process of the frontal lobe (FL) in primates, the reduction of type b Lamin drives the activation of endogenous retroviruses (ERVs), which in turn activate cGAS and exacerbate neuroinflammation in the aging brain [51].

YAP and TAZ are transcriptional co-activators that regulate the expression of genes downstream of mechanical signaling. When cells experience mechanical signals, such as changes in substrate stiffness or tension, these

signals are perceived by integrins and other mechanical receptors on the cell surface, thereby leading to a series of intracellular signaling events [109]. cGAS-STING signaling is inhibited by YAP/TAZ mechanotransduction. It has been shown that YAP is downregulated and inactivated in hippocampal astrocytes of aging mice [110], whereas TAZ target genes are similarly downregulated in aged mouse and human brains [111]. Loss of YAP/TAZ function leads to loss of nuclear integrity and promotes senescence and inflammation through activation of the cGAS- STING pathway [112].

Impaired clearance of cytoplasmic DNA

Mitochondrial autophagy (cGAMP) is a specific type of autophagy that targets and removes damaged mitochondria, and in the context of neuroinflammation, mitochondrial autophagy is key to maintaining the health of neurons and glial cells [113]. Mitochondrial autophagy is closely related to the negative regulation of the cGAS-STING pathway, which is inhibited in the mouse hippocampus through degradation of mtRNAs [114]. Impaired mitochondrial autophagy is likewise one of the hallmarks of aging. In general, when the accumulation of damaged mtDNA in mitochondria exceeds the capacity of the repair system, mitochondria are selectively degraded by autophagy, and then mtDNA is degraded by DNase II in lysosomes; however, in older individuals, increased oxidation of mtDNA can lead to saturation of DNase II, so that the mtDNA fragments will be spared from degradation and released into the cytoplasm [102]. In addition to causing mtDNA, impaired autophagy likewise delays the clearance of activated STING, leading to dysregulation of the negative feedback mechanism of the cGAS-STING pathway. Nicotinamide adenine dinucleotide (NAD^+) is an important factor in the regulation of mitochondrial autophagy, and it inhibits the cGAS-STING pathway in a manner that induces mitochondrial autophagy. The overall decrease in NAD^+ levels in cells with age leads to defective mitochondrial autophagy, allowing more mtDNA to be released into the cytoplasm, providing more opportunities for cGAS-STING activation [104]. p-Ub protein accumulates in the hippocampus even in healthy older adults, indirectly reflecting increased mitochondrial damage and or decreased mitochondrial autophagic flux during aging [85]. Defective mitochondrial autophagy is also thought to play a role in the pathogenesis of other neurodegenerative diseases such as Alzheimer's disease, and drugs that promote and induce mitochondrial autophagy may have considerable therapeutic potential in these age-related diseases [5, 49].

Chromatin spillover triggered by loss of structural stability of the nuclear membrane induces activation of the cGAS-STING pathway by a mechanism involving aberrant localization of cGAS in cytoplasmic chromatin regions and decline in DNA damage repair capacity (Fig. 1) [105]. In the physiological state, nucleases such as DNase2 and TREX1 are responsible for the removal of double- and single-stranded DNA from the cytoplasm, thereby maintaining immune homeostasis [108], whereas caspase-3/–7 blocks its recognition of mitochondrial DNA by cleaving cGAS during apoptosis [29, 115]. However, the decline in nuclease expression that occurs with age significantly impairs cytoplasmic DNA scavenging, leading to abnormal accumulation of nuclear-derived genetic material in the cytoplasm [10, 31]. This dysfunction of the clearance system makes it easier for cGAS to capture chromatin fragments escaping to the cytoplasm, which in turn initiates a pro-inflammatory signaling cascade. Studies of the mechanisms involved have shown that the breakdown of nuclear membrane integrity in senescent cells results in the rupture of micronuclear structures, which are an important source of cytoplasmic DNA, and that the failure of nuclease to remove this spilled genetic material in a timely manner continues to activate the neuroinflammatory process mediated by the cGAS-STING pathway [105].

Activation of the cGAS-STING pathway secondary to other age-related diseases

Activation of the cGAS-STING pathway is a key mechanism of neuroinflammation triggered by traumatic brain injury (TBI) [116]. Post-trauma-induced neuroinflammatory responses become more intense and detrimental with age. cGAS protein expression in the injured cortex of aged mice was significantly increased by TBI. This age-related activation of cGAS may be a mechanistic link between microglial-associated neuroinflammation and neurodegeneration in the aged TBI brain [117].

Older mice exhibit stronger upregulation of cGAS after cerebral hemorrhage (ICH) compared to younger mice. The cumulative effects of aging and cerebral hemorrhage lead to the production of dsDNA, which activates the cGAS-STING pathway and accelerates neuroinflammation. li et al. demonstrated that cGAS, ZBP1, and IFN-β mRNA expression was increased in old mice after ICH, but not after ICH in young mice, whereas RNAseq analyses targeting both young and old traumatic brain injury mice revealed age-related upregulation of cGAS and IFN-I, and the phenomenon was closely associated with microglial-mediated neuroinflammation [118], providing a rationale for the activation of the cGAS-STING pathway secondary to ICH in older individuals.

Ischemic stroke is a debilitating neurological disorder that causes elevated neuroinflammation, and aging is the greatest risk factor for ischemic stroke [119, 120]. The cGAS pathway is activated during ischemic stroke, In a mouse model of ischemic stroke, cerebral ischemia leads to the release of dsDNA into the cytoplasm, while

extensive tissue necrosis results in the accumulation of large amounts of cytoplasmic DNA and triggers subsequent inflammatory responses through activation of the cGAS pathway [121]. Huang et al. further explored the mechanisms involved in a recent study, proposing that cerebral ischemia caused by ischemic stroke promotes ceramide production in astrocytes, which is lipotoxic and promotes the release of mtDNA into the cytoplasm by disrupting the integrity of the mitochondrial membrane and triggering cGAS-STING pathway-dependent interferon responses [122].

Increased prevalence of type 2 diabetes mellitus (T2DM) in older age groups [123]. T2DM is significantly affected by age due to factors such as decreased beta cell numbers. Whereas diabetes-related metabolic syndrome leads to cognitive decline, glial cell activation and increased incidence of neuroinflammation, T2DM-related metabolic and lipotoxic stress leads to mitochondrial damage and mtDNA leakage into the cytoplasm, which further initiates cGAS activation and its downstream IFN-I response, leading to diabetes-associated central neuroinflammatory alterations and cognitive impairment [124, 125].

Herpes simplex virus type 1 (HSV-1) is a neurophilic virus that has an infection rate of up to 90% in the population and can remain latent in the organism for life. After primary infection of epithelial cells, the virus can metastasize to reach the cell bodies of peripheral nervous system (PNS) ganglia and establish latent infection [126]. Aging can lead to the possible reactivation of latent HSV-1 in the body. As the immune system weakens in later life, HSV1 can enter the brain via the trigeminal nerve and other pathways, causing inflammation and cellular changes that promote amyloid production and other changes. In vitro experiments have confirmed that HSV-1 infection triggers neurons to develop pathological changes characteristic of AD, such as abnormal Aβ deposition and pathological phosphorylation of tau proteins, as well as activation of Alzheimer's disease-associated inflammatory signaling networks. Among the antiviral defense mechanisms, the IFN-I signaling pathway has a central regulatory role in HSV-1 infection [127, 128], in which microglia, as a major source of type I IFN production within the CNS, have been found to have a significant correlation between their pro-inflammatory factor secretion process and the activation of the cGAS-STING signaling pathway [129].

Downstream of cGAS-STING pathway in neuroinflammation and neurodegenerative diseases

As mentioned earlier, the downstream pathways of the cGAS-STING pathway involve multiple branches. Among them, the activation of interferon type I (IFN-I) and nuclear factor κB (NF-κB) pathways are two important pathways leading to inflammation. There are differences in the ways they trigger inflammation, but both can promote the increase of various age-related secreted phenotypes (SASPs). It is worth pointing out that the relationship between SASP and aging has a dynamic bidirectional role. On the one hand, senescence is a trigger for SASP: after the cGAS-STING pathway is activated by multiple senescence-related factors, its downstream IFN-I and NF-κB pathways can upregulate SASP. in addition, senescent individuals can also initiate SASP expression through multiple signaling pathways such as p38 MAPK [130]. On the other hand, SASP further accelerates senescence and promotes systemic aging and disease: while early on some SASP components may play a protective role through immune modulation, the pro-inflammatory and pro-aging effects of SASP become predominant with the accumulation of senescent cells, and the chronic inflammation induced by SASP is capable of further damaging DNA, which is manifested in the brain by neuronal damage, synaptic loss, and reduced cognitive function. More importantly, SASP induces senescence in other cells through autocrine and paracrine effects, which promotes more SASP secretion and tissue dysfunction [131, 132], which further exacerbates the vicious cycle of senescence.

IFN-I

Interferon type I (IFN-I) is a class of cytokines that includes IFNα, IFNβ, IFNε, IFNκ, and IFNω, and IFN-I induces the production of a variety of inflammatory factors in the brain and mediates neuroinflammation in the central nervous system [133]. The cGAS-STING pathway drives deleterious IFN-I activation in a variety of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease [61, 134].

IFN-I signals through the heterodimeric receptor IFNAR and the JAK/STAT signaling cascade, a cascade that leads to the secretion of pro-inflammatory cytokines and chemokines as well as more IFNs by the following mechanism [135]: IFN-I binds the IFN-I receptor (IFNAR) extracellularly, and the intracellular portion of the IFNAR binds to two tyrosine kinases, JAK1 and Tyk2. Upon binding, IFNAR then attracts STAT1 and STAT2 for binding and phosphorylation modification of STAT1 and STAT2 by JAK1 and Tyk2. Subsequently, STAT1 and STAT2 bind interferon regulatory factor 9 (IRF9) to form a heterotrimeric transcription factor complex called interferon-stimulated gene factor-3 (ISGF3) [136]. ISGF3 can drive the transcription of ISGs by binding to genes containing interferon-sensitive response elements (ISREs), including antiviral proteins, chemokines (such as CXCL10 and CCL5), and IFN-I itself [137]. Under chronic stress conditions, the JAK/STAT signaling

cascade generates large amounts of reactive oxygen species, resulting in damage to the mitochondrial membrane and the subsequent release of mtDNA into the cytoplasm [70], which in turn provides for the activation of the cGAS-STING pathway.

Activation of the IFN-I pathway is a protective mechanism against brain aging. Appropriate activation enhances the brain's resistance to viral infections but has deleterious effects on brain function and cognition under certain conditions; patients with persistently elevated IFN-I exhibit autoinflammatory disease in multiple organs, including the brain, and the deleterious effects of inflammation are particularly pronounced in the context of aging [69, 138, 139].

Due to high responsiveness to IFN-I, microglia were the first brain cells to detect age-dependent IFN-I signaling [140]. Interferon-responsive microglia are a subpopulation of microglia that can cause widespread tissue inflammation upon activation by cGAS-STING. Interferon-responsive microglia accumulate up to 20–40% of the total in different brain regions of aged mice [133] and IFN-I-reactive microglia-driven neuroinflammation and neuronal loss of function in mouse models of AD have been demonstrated experimentally [141], these microglia promote the progression of neurodegenerative diseases by releasing pro-inflammatory factors, disrupting synapses, and phagocytosing and clearing Aβ plaques, and the extracellular IFN-I they produce further maintains the highly activated state of the microglia themselves [64].

Selective ablation of IFNAR1 from microglia in aged mice significantly inhibited microglia reactivity, attenuated neuronal loss, and reduced lipofuscin accumulation, a central feature of neuronal aging [141], and other ways of blocking IFN-I signaling in the brains of aged mice have also been reported to reduce microglia proliferation, attenuate aging-associated chronic neuroinflammation, and partially restore cognitive function and hippocampal neurogenesis [128, 138].

Microglia after IFN-I response induced by the STING signaling pathway showed enhanced chemokine signaling such as CCL5 and CXCL10 [48, 142]. Sustained excess chemokine production may trigger deleterious effects on neuronal function and the CNS microenvironment, such as CXCL10-CXCR3 signaling that regulates microglia recruitment and dendrite loss after axonal injury [143]. Furthermore, microglia-derived CCL5 leads to autophagy inhibition and protein aggregation accumulation in a mouse model of Huntington's disease through activation of neuronal CCR5 [48]. The IFN-I response in microglia also leads to loss of cognitive resilience by decreasing myocyte enhancer factor 2c (MEF2C) transcription in neurons [71].

Other brain cells responsive to IFN-I, such as neurons, astrocytes, oligodendrocytes, meningeal immune cells, and endothelial cells, have also been detected in brain aging and disease conditions [133]. IFN-I alters neuronal structure and function by releasing pro-inflammatory cytokines, leading to activation of neurodegeneration-related pathways [144, 145]. Dendritization of rat primary neurons is significantly impaired with increasing doses of IFN-α treatment [146]. Mice with overexpression of IFN-α exhibited inflammation-related pathological changes, including lymphocyte inflammatory cell infiltration, vascular alterations, brain calcification and neurodegeneration [147]. Chronic IFN-β exposure, in turn, triggers DNA damage, p53 pathway activation, and senescence [58]. In addition, a study conducted by Baruch et al. demonstrated that aging-associated cognitive decline in aged mice is associated with excess IFN-I signaling and found that IFN-I signaling in the choroid plexus promotes age-dependent cognitive decline [138].

NF-κB

NF-κB is one of the key SASP regulators, and its mediated immune response becomes an important source of brain aging, while the cGAS- STING signaling pathway can initiate the NF-κB pathway [39].

NF-κB, as a core transcription factor regulating immune response, promotes immune system regulation by mediating cell survival, proliferation and activation of inflammation-related genes. Studies have shown that the expression of a large number of pro-inflammatory factors in senescent cells is dependent on the transcriptional regulation of NF-κB, and that its sustained activation plays a key pivotal role in the neuroinflammatory cascade response [148–151]. In glial cells, NF-κB, after nuclear translocation through the IKK/IκB signaling axis, binds to the κB binding sites in the promoter regions of inflammatory factor genes such as IL-6, TNF-α, and IL-1β and promotes their transcriptional expression, a mechanism that exacerbates neuroinflammatory responses in autoimmune encephalomyelitis, ischemic injuries, and AD, among other pathologies [152]. Notably, chronic NF-κB activation increases neuroinflammation and neuronal cell death, promotes reactive oxygen species generation by upregulating the expression of enzymes such as COX-2 and iNOS, and enhances the secretion of chemokines CCL2/MCP-1, which together lead to neuronal apoptosis and synaptic dysfunction [153, 154]. In astrocytes, NF-κB can regulate the expression of complement system component C3 and promote the release of chemokines, thereby recruiting peripheral immune cells to exacerbate inflammatory damage [155], whereas chronic activation of NF-κB in oligodendrocytes triggers impaired synthesis of myelin proteins, which is characterized by abnormally high levels of the SASP factor and progressive damage to

the white matter structure, a pathological change that are closely associated with the decline of motor learning ability [151].

NLRP3 is a PRR in the NLR family. cGAS-STING may directly or indirectly activate NLRP3 in multiple ways and promote the progression of neurodegenerative diseases [156]. Among them, NF-κB is closely related to the activation of the NLRP3 inflammasome [149, 157]. It has been reported that STING may control NLRP3 induction by activating SYK and SYK-triggered reactive oxygen species synthesis, or cause lysosomal damage and induce K + efflux, thereby activating the NLRP3 inflammasome [158, 159]. NLRP3 consists of the immune receptor protein, the articulin ASC, and the inflammatory protease caspase-1, and the activation of these components by the cGAS-STING pathway leads to the release of IL-1β, which further releases pro-inflammatory cytokines, chemokines, and IFN-I, triggering neuroinflammation, oxidative stress, and neuronal injury [160, 161]. NLRP3 inflammasomes activated by the cGAS-STING pathway have also been found to promote microglial cell pyroptosis [158], and aberrant NLRP3 inflammasome activity triggers downstream signaling dysregulation, which underlies a wide range of CNS disorders [162].

Interactions between different CNS cells

As core immune cells of the central nervous system, microglia are important bearers of SASP regulation in the brain [163]. Microglia maintain a resting state under physiological conditions and can be rapidly activated in response to injury or pathological stimuli to maintain neurohomeostasis by removing abnormal protein aggregates and initiating innate immune responses [164, 165]. However, persistent stress can lead to abnormal secretion of neurotoxic mediators such as nitric oxide, IL-1β, and TNF-α, creating a microenvironment in the brain that promotes the development of neurodegenerative lesions [166].

Cellular senescence is a trigger for microglia to upregulate SASP [167]. As mentioned earlier, the cytoplasmic DNA accumulated by senescent microglia is recognized by cGAS and stimulates the activation of microglia, releasing a large amount of pro-inflammatory cytokines, which leads to neuroinflammation and aggravates neurotoxicity, causing neurodegeneration and cognitive decline. Corresponding anti-aging treatments or systemic elimination of senescent cells can effectively reduce the activation of microglia and reverse the damage induced by SASP [168].

The factors that activate microglia are further complicated in the context of neurodegenerative diseases. In the early stages of neurodegenerative disease development, the body's compensatory mechanisms for inflammatory injury are still able to function. In advanced stages of neurodegenerative diseases, multiple stimuli, including increased cellular senescence, increased leakage of mitochondrial DNA and nuclear DNA, autophagy defects, and cell death, as well as microbial and exogenous DNA, can activate the cGAS-STING pathway and promote the secretion of high levels of pro-inflammatory cytokines by microglia, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which are components of the senescence-associated secretory pattern (SASP).These cytokines trigger cytotoxicity, acute immune response and rapid inflammatory response, causing neuronal damage and disrupting the integrity of the blood-brain barrier [23]. In particular, TNF-α can activate microglia and astrocytes and induce ROS production, thereby damaging neurons and synapses; it can also promote the phosphorylation and aggregation of tau proteins to form neurotoxic oligomers and fibers, or impair synaptic transmission and plasticity by affecting the expression and function of the AMPA receptor [169]. Excessive brain TNF concentrations are important in the pathogenesis of neurodegenerative diseases [170]. TNF plays an important role in the propagation of inflammation by activating and recruiting immune cells through its receptor TNFR1. In addition, TNFR1 can directly induce oxidative stress through activation of ROS- and RNS-producing enzymes, which together with neuroinflammation promote neurodegeneration [171]. Using CgasR241E transgenic mice, Gulen et al. observed impaired learning ability and neuronal density in the hippocampus associated with neuronal function and detected upregulation of TNF in interferon-associated microglial cell states in CgasR241E mice. Addition of a neutralizing anti-TNF antibody rescued CgasR241E-induced neuronal death, whereas blockade of IFN-I signaling was ineffective, suggesting a critical role for TNF associated with aberrant cGAS activity in impairing neuronal survival [47].

Although it is now widely accepted that microglia are the primary functional cells expressing the cGAS–STING pathway in the central nervous system, some studies suggest that astrocytes and even neurons may also participate in the activation of this pathway under certain pathological conditions. Astrocytes are the most numerous and widely distributed class of glial cells in the central nervous system, maintaining the balance of the neural microenvironment by regulating synaptic plasticity, metabolic homeostasis and blood-brain barrier function [172]. Studies in aging models such as A- T have shown that senescent astrocytes are also capable of inducing pro-inflammatory responses in a cGAS-STING-dependent manner, driving the loss of functional neurons and promoting neurotoxicity and neurodegeneration. Other reports have shown that STING- and TBK1-positive astrocytes can be observed in the putamen and

substantia nigra of patients with Parkinson's-type multiple system atrophy (MSA-P), suggesting that activation of the cGAS–STING pathway in astrocytes may promote disease progression [173].

As a core functional unit of the central nervous system, neurons are particularly susceptible to the effects of abnormal protein aggregation, oxidative stress, and inflammatory microenvironments [174]. Previous studies have suggested that activation of the cGAS–STING pathway in motor neuron samples from patients with amyotrophic lateral sclerosis (ALS) may be associated with inflammation-related damage, but its cellular origin and functional specificity remain to be further verified. Neurons can limit microglia overactivation under resting brain conditions by releasing a variety of inhibitory factors, such as the chemokine CX3CL1, which inhibits microglia activation and reduces their expression of inflammatory factors by binding to the receptor CX3CR1 on microglia. With the progression of aging and AD, a significant reduction of CX3CL1 in the hippocampus accompanied by a decrease in CX3CR1 expression may exacerbated microglia neurotoxicity [82].

Activation of microglia can cause a series of secondary changes in other cells of the CNS. As key links in neurotoxic signaling, astrocytes and neurons may participate in the propagation of neuroinflammation through specific mechanisms based on the activation of microglia. It has been shown that increased formation of damaged mitochondria in activated microglia, which are released from these cells and targeted to neighboring astrocytes and neurons, exacerbates astrocyte activation and neuronal death and contributes to the propagation of neurodegenerative signals [175]. Astrocytes exhibit a remarkable functional transformation into reactive astrocytes in the setting of chronic neuroinflammation. And reactive astrocytes form a positive feedback regulatory mechanism with the initial microglia-mediated inflammatory response by further releasing large amounts of inflammatory mediators [172]. Liddelow et al. demonstrated that activated microglia induce the formation of a reactive astrocyte subtype A1 ex vivo through the secretion of key factors, such as IL-1α, TNF and C1q. This subtype has a toxic function in inducing neuronal and oligodendrocyte death and shows significant enrichment in pathological tissues of major neurodegenerative diseases such as AD, PD, and ALS [176]. Whereas, at the molecular level, microglia-derived TNF-α and IL-1β significantly enhance the catalytic activity of NO synthase 2 (iNOS) in astrocytes, leading to an increased production of nitric oxide (NO) and its highly reactive reaction products with superoxide peroxynitrite (ONOO-), which induces oxidative stress while activating other neurodegenerative pathway [93].

Abnormal activation of the cGAS-STING pathway in brain endothelial cells (BECs), a component of the blood-brain barrier, constitutes one of the important regulators of neuroinflammation. During aging, mitochondrial dysfunction in the vasculature leads to the release of mtDNA into the cytoplasm, while nuclear DNA damage increases the number of cytoplasmic chromatin fragments. These processes can activate the cGAS-STING pathway in endothelial cells, leading to endothelial dysfunction associated with aging. cGAS-STING pathway-mediated activation of IFN signaling in BECs can lead to neurovascular inflammation and leakage of the blood-brain barrier through a variety of mechanisms, resulting in dysfunction of the neurovascular unit and hypoxia, which amplifies inflammatory responses within the central nervous system, leading to neuronal Dysfunction and injury [177]. Thus, IFN-I produced by BECs, together with interferon secreted by microglia, astrocytes, and neurons, constitutes a networked inflammatory regulatory system that amplifies the local inflammatory response through synergistic action and drives the pathological process of neurodegenerative diseases.

cGAS-STING pathway modulators

Since the cGAS-STING pathway has been identified as a significant driver in various neurodegenerative diseases, exploring strategies for targeted intervention against this pathway holds potential therapeutic value for multiple neurodegenerative disorders. Beyond conventional pharmacological interventions, gene editing technologies such as CRISPR-Cas9, capable of correcting genes associated with dysfunctional mitophagy or aberrant pathway activation, have also demonstrated promising application prospects [178]. Modulators of the cGAS-STING pathway can be categorized based on their mechanism of action as follows (Table 1):

Indirect modulators

Reducing or clearing cytosolic DNA fundamentally prevents the activation of cGAS and its downstream signaling. Some modulators reduce mtDNA leakage by regulating mitochondrial homeostasis. For instance, Yang et al. demonstrated that clearing mtDNA released into the cytosol using Mdivi-1, or blocking mtDNA release via mPTP-VDAC channel inhibitors, attenuated sevoflurane-induced cytosolic escape of mtDNA, thereby reducing cGAS-STING pathway activation in microglia [159]. Another study reported that Tetrahydroxystilbene glucoside (TSG), a natural active component from Polygonum multiflorum, may reduce the accumulation of cytosolic DNA fragments and inhibit cGAS-STING signaling pathway activation. Consequently, it decreased NLRP3 expression in the hippocampus and peripheral inflammatory factor levels in APP/PS1 mice, significantly

Table 1 cGAS-STING pathway modulators.

	Name	Type	Target	Effect	References
Direct modulators	RU.521	Cyclic dinucleotide analogues	cGAS	Occupies the catalytic site of cGAS, reducing its affinity for ATP and GTP	[189]
	Aspirin	Acetylsalicylic acid	cGAS	Induces acetylation of cGAS, restricting the infiltration of immune cells such as neutrophils, dendritic cells, and macrophages	[196]
	H-151	Small-molecule compounds containing acrylamide group	STING	Irreversibly modifies the Cys91 residue of STING, inhibiting STING palmitoylation	[191]
	C-176	Small-molecule derivatives of nitrofuran	STING	Covalently modifies the Cys91 residue of STING, inhibiting STING palmitoylation	[191]
	Punicalin (PUN)	Polyphenolic compounds derived from ellagitannins in pomegranate fruit	cGAS-STING signaling pathway	Inhibits the cGAS-STING signaling pathway, reduces D-galactose-induced ROS damage and neuroinflammation, suppresses microglial activation and astrocyte proliferation, and ameliorates hippocampal damage in aged mice	[90]
	Semen Strychni pulveratum (SSP) and vomicine	SSP: Processed product derived from the seeds of *Strychnos nux-vomica* L.; Vomicin: The principal bioactive alkaloid component of *Strychnos* seeds (SS)	cGAS, STING, TBK1, et al.	Inhibits the activation of the cGAS-STING-TBK1 pathway, downregulating protein and mRNA levels of cGAS, STING, TBK1, and IRF3; improves motor function, weight loss, gastrocnemius muscle atrophy, and motor neuron loss in an ALS model	[74]

Table 1 (continued)

	Name	Type	Target	Effect	References
Indirect modulators	Mdivi-1	Small-molecule DRP1 inhibitor	mtDNA	Inhibits DRP1 to reduce mitochondrial membrane potential loss and blocks mtDNA release into the cytosol	[159]
	CsA (Cyclosporine A)	Small-molecule mPTP inhibitor	mtDNA	Suppresses mPTP channel opening, reducing sevoflurane-induced mtDNA release into the cytosol	[159]
	VBIT-4	VDAC oligomerization inhibitor	mtDNA	Inhibits VDAC channel oligomerization, blocking sevoflurane-induced mtDNA release into the cytosol	[159]
	Tetrahydroxy stilbene glucoside (TSG)	Natural stilbene glycosides derived from *Polygonum multiflorum*	Cytosolic DNA	Reduces cytosolic DNA accumulation, suppresses cGAS-STING pathway activation, and decreases NLRP3 inflammasome activity; promotes microglial transition from pro-inflammatory M1 phenotype to resting M0 state, improving learning and memory in AD model mice	[179]
	nicotinamide riboside (NR)	Vitamin B3 derivatives	mtDNA	Elevates intracellular NAD^+ levels, induces mitophagy to clear damaged mitochondria, and reduces cytosolic DNA accumulation; attenuates microglial and astrocyte activation, improving cognitive function and synaptic plasticity in AD model mice	[180]
	Fibroblast growth factor 4(FGF4)	Recombinant protein growth factor	cGAS-STING pathway-associated proteins	Downregulates cGAS-STING pathway-related proteins (RAB2B, XRCC5, XRCC6) and mTOR signaling, reduces astrocyte activation, and ameliorates neuroinflammation and functional impairment in ALS models	[24]
	FGF21	Recombinant protein growth factor	mtDNA	Induces mitophagy in an AMPK-dependent manner, reduces mtDNA release into the cytosol, and inhibits cGAS-STING pathway activation	[181]
	Urolithin A(UA)	Natural benzimidazolones	mtDNA	Triggers PINK1-dependent mitophagy to eliminate damaged mitochondria, decreases cytosolic mtDNA leakage, and operates without inducing cytotoxicity	[59]
	Brefeldin A	Macrolide fungal metabolites	ARF1	Inhibiting ARF1 function disrupts Golgi apparatus structure and vesicle trafficking, blocking the anterograde transport of STING from the endoplasmic reticulum to the Golgi apparatus	[182]
	c-Jun peptide	Synthetic peptides	c-Jun	Inhibiting c-Jun phosphorylation reduces RNA-DNA hybrid formation, thereby suppressing cGAS-STING pathway activation and caspase-3-mediated apoptosis	[77]
	GSK-650,394	Small-molecule kinase inhibitors	SGK1 kinase	Downregulating the cGAS-STING pathway by inhibiting SGK1 kinase activity alleviates mitochondrial stress in glial cells and neuroinflammation	[183]
	Anti-EGLN2 Morpholino Oligonucleotide(AMO)	Antisense oligonucleotides	EGLN2	Specific knockdown of EGLN2 expression reduces ROS-induced mtDNA release and inhibits cGAS-STING pathway activation; it improves motor neuron function in the SOD1G93A ALS model	[184]
	Thiamet-G	Aminoglycoside analogues	STING	Selective inhibition of O-GlcNAcase (OGA) enzyme activity upregulates O-GlcNAcylation levels on STING, competitively reducing its phosphorylation levels	[187]
	AAV9-Sptlc2 shRNA	shRNA	Sptlc2	Downregulating Sptlc2 in the brain reduces ceramide-induced disruption of mitochondrial membranes and the release of mtDNA	[122]

improving their cognitive dysfunction [179]. Treatment with the NAD + precursor nicotinamide riboside (NR) reduced mtDNA accumulation in the cytosol by inducing mitophagy, normalizing the elevated cGAS-STING observed in AD mice [180]. Fibroblast growth factor 4 (FGF4) reduced proteins associated with mitochondrial dysfunction, reversing astrocytic dysfunction and reactivity in ALS [24]. The mitophagy inductor urolithin A lowered cytosolic mtDNA levels, diminished cGAS-STING activation and neuroinflammation, and alleviated age-related neurological decline, including improvements in synaptic connectivity, cognitive memory, and visual function [59]. Ma et al. found that FGF21 intervention promotes mitophagy in an AMP-activated protein kinase (AMPK)-dependent manner, thereby preventing

mtDNA release into the cytosol and inhibiting cGAS-STING pathway activation [181].

The cGAS-STING signaling pathway has multiple regulatory factors. With further research on the relevant mechanisms, indirectly influencing the activity of the cGAS-STING pathway through these regulatory factors is expected to become a feasible anti-inflammatory strategy. For instance, GTPase ADP-ribosylation factor 1 (ARF1) is a critical negative regulator of cGAS-STING signaling. Complete disruption or depletion of ARF1 using agents like Brefeldin A attenuates STING-dependent signaling [182]. In AD models, upregulation of c-Jun activates the cGAS-STING pathway and triggers neuroinflammatory responses. Employing c-Jun inhibitors effectively blocks this activation, significantly ameliorating neuronal death and impaired neurogenesis in AD progenitor cells. Furthermore, developing nanobody-based RNA-DNA hybrid targeting strategies may circumvent common side effects associated with conventional anti-inflammatory drugs [77]. Upregulation of serum/glucocorticoid-regulated kinase 1 (SGK1) participates in the progression of multiple neurodegenerative diseases. Application of SGK1 inhibitors, such as GSK-650,394, not only downregulates the expression of key components of the cGAS-STING pathway in glial cells but also alleviates oxidative stress and mitochondrial stress in neuronal cells, rescues pathological α-syn accumulation and PD-associated behavioral deficits, suggesting it as a potential effective strategy for treating PD and other neurodegenerative disorders [183]. Recent studies revealed that the Egl-9 family hypoxia-inducible factor (EGLN) enzyme EGLN2 mediates interferon inflammatory responses in astrocytes and exacerbates motor neuron degeneration in ALS by regulating the cGAS-STING pathway. Pharmacological inhibition of EGLN2 using AMO or CRISPR-Cas9-mediated EGLN2 deletion reduces neuroinflammation and restores motor neuron function, highlighting its potential as a therapeutic target for ALS [184]. O-GlcNAcylation is a post-translational modification specifically occurring on serine or threonine residues. O-GlcNAcylation within the gene promoter region of PINK1, a mitophagy-related protein, was found to upregulate PINK1 expression [185]. Another study demonstrated that elevated O-GlcNAc levels activate the integrated mitochondrial stress response, promote the expression of the mitophagy-associated protein LC3, and enhance PINK1 function through direct modification, thereby facilitating the clearance of dysfunctional mitochondria and reducing aberrant cytosolic mtDNA accumulation [186]. Research by Zhu S et al. demonstrated that upregulation of O-GlcNAcylation via Thiamet-G (TMG) competitively reduces phosphorylation levels on the STING protein. This blocks the activation of STING and its downstream inflammatory pathways, and ameliorates cognitive dysfunction in PD mouse models [187].

For the activation of the cGAS-STING pathway caused by diseases prevalent among the elderly, targeting disease-related triggers upstream of the cGAS-STING pathway is a viable strategy. In mouse models of ischemic stroke, intracerebral injection of AAV9-Sptlc2 shRNA to downregulate Sptlc2 in the brain reduced ceramide production. This decrease in ceramide minimized mitochondrial membrane disruption and the subsequent release of mtDNA, leading to a concomitant reduction in the cGAS-STING pathway-dependent interferon response [122]. Furthermore, transplantation of mesenchymal stem cells (MSCs) pretreated with an iron-quercetin complex (IronQ) suppressed the protein expression levels of the cGAS-STING signaling pathway. This intervention effectively mitigated neurological deficits and neuroinflammation by modulating microglial polarization, thereby alleviating inflammatory damage following intracerebral hemorrhage [188].

Direct modulators

Compared with broad-spectrum anti-cytokine antibodies or targeted drugs of other signaling molecules, modulators that directly regulate the cGAS-STING pathway have demonstrated more significant therapeutic advantages in some animal models and in vitro experiments [189–192]. These modulators, while alleviating neuroinflammation and improving cognitive function, retain compensatory innate immune recognition pathways, thus being less likely to cause the disorder of normal immune surveillance that is often associated with traditional anti-inflammatory therapies [105].

Activation of cGAS is dependent on the binding of cytoplasmic DNA, and cGAS inhibitors inhibit inflammatory triggering at the initiation of the pathway by blocking the binding of cGAS to DNA or inhibiting its catalytic activity and reducing the production of cGAMP. RU.521, a commonly used cGAS inhibitor, is able to competitively bind to the DNA-binding domain of cGAS, blocking its interaction with double-stranded DNA [189]. Blocking cGAS using RU.521 attenuates cognitive dysfunction induced by cGAS-STING activation in a mouse model and attenuates microglia inflammation mediated by activation of its downstream NLRP3 inflammasome [159].

STING antagonists directly target STING proteins and inhibit their oligomerization or downstream signaling. Receipt of STING inhibitors attenuated inflammatory markers in the periphery and brain of naturally aging mouse models, significantly enhancing their spatial and associative memory. For example, administration of the STING inhibitor H-151 to aged mice decreases microglia levels, attenuates astrocyte immunoreactivity, blocks

neuronal loss in the CA1 region of the hippocampus, and increases levels of synaptic activity, and knockdown of the STING gene exerts similar effects [47, 191]. C-176 significantly ameliorates dopaminergic neuronal damage and motor dysfunction in MPTP-induced models by inhibiting STING and blocking downstream signaling, and reduces inflammatory responses and prevents M1 polarization of BV2 microglia [191, 193, 194]. However, STING antagonists such as these have poor blood-brain barrier permeability and lack clinical trials, and therefore do not yet have clear therapeutic significance. Notably, a recent study constructed an amphiphilic copolymer self-assembled nanomedicine based on a synergistic combination of an artificial nanoribonuclease and a STING inhibitor, C-176, which combines DNA scavenging and targeted inhibition of STING to effectively attenuate neuroinflammation and protect ischemic hemidiaphragm neurons, providing a new idea for balancing the central immune homeostasis and improving the prognosis of stroke [195]. In addition to H-151 and C-176, inhibition of cGAS activitie using aspirin in a brain-like organ model of premature aging was effective in attenuating senescent astrocyte-driven inflammation, and this efficacy has the same potential to be generalized to a number of neurodegenerative disorders [11].

Other modulators such as PUN, which mainly exists in the peel, seeds and leaves of pomegranates, can inhibit the expression of cGAS, p-Sting, p-TBK1, p-p65, and p-IRF3 in the brains of aged mice and in vitro-cultured BV2 microglia, and improves cognitive dysfunction in aged mice through antioxidant and anti-inflammatory mechanisms, potentially serving as a therapeutic agent for brain aging and age-related diseases [90].Semen Strychni pulveratum (SSP) and vomicine exhibit neuroprotective and anti-neuroinflammatory effects in the treatment of ALS. Both modulate neuroinflammation via the cGAS-STING-TBK1 pathway, protecting neuronal function in ALS patients and demonstrating potential to prevent muscle atrophy [74].

Conclusion and perspectives

Inflammation serves as a bridge connecting aging and age-related diseases. Chronic neuroinflammation is not only a hallmark of normal brain aging but also a driving force in the progression of neurodegenerative diseases. Recent research has well-established that, with the involvement of aging-related factors, the cGAS-STING pathway senses aberrantly accumulated cytosolic DNA, inducing the senescence-associated secretory phenotype (SASP) and driving aging-associated neuroinflammatory responses.

The intricate cellular composition of the central nervous system (CNS) presents significant challenges in studying the underlying mechanisms. Neuroinflammation within the CNS involves the intricate interplay of multiple cell types, including neurons, glial cells, and endothelial cells. Particularly in the context of aging, alterations in various physicochemical factors and signaling pathways within the brain mean that numerous aging-related factors can directly or indirectly lead to cGAS-STING pathway activation. Although this review speculates on some potential mechanistic links, direct evidence for the role of these mechanisms in cGAS-STING activation within the aging brain is still lacking.The cGAS-STING pathway exhibits complex commonalities and specific characteristics in driving the progression of different neurodegenerative diseases. On one hand, the excessive activation of cGAS-STING caused by aging-related changes, through driving neuroinflammation, constitutes a shared pathological basis for various neurodegenerative diseases. On the other hand, the activating factors and downstream effects of the cGAS-STING pathway display certain variations across different neurodegenerative diseases. Furthermore, the activation patterns and effects of the cGAS-STING pathway may differ depending on the specific brain region and cell type. Certain brain regions, such as the hippocampus and frontal lobe, which are metabolically active and susceptible to oxidative damage, may be more prone to cGAS-STING activation due to DNA damage. Regarding different brain cells, although cGAS-STING activation is most prominent in microglia, the molecular mechanisms underlying transcellular crosstalk among other CNS cell types—such as astrocytes, neurons, oligodendrocytes, and vascular endothelial cells—play a significant and non-negligible role. Moreover, the relative impact of different mechanisms within the cGAS-STING pathway may vary depending on disease type, stage of aging, and individual differences, making it difficult to definitively pinpoint which specific mechanisms are the core drivers of neurodegeneration.

Although targeted inhibitors against key nodes of the cGAS-STING pathway and its upstream/downstream components have shown potential therapeutic value in preclinical models, the current understanding of this pathway remains insufficient to support the design of precise therapeutic strategies. It is worth noting that the cGAS-STING pathway plays an important role in innate immune surveillance and antitumor responses, while aging is also an important risk factor for tumorigenesis. Therefore, when implementing cGAS-STING inhibition strategies for neurodegenerative diseases in the elderly population, it is necessary to be vigilant about the potential risk of weakened tumor immune surveillance and to strike a balance between neuroprotection and systemic tumor risk in individualized treatment. Additionally, most existing cGAS-STING pathway inhibitors lack cell specificity and may pose risks due to their broad inhibition of other cellular functions. Many small-molecule

inhibitors, such as the STING antagonist C-176, struggle to effectively penetrate the blood-brain barrier (BBB). Furthermore, the safety concerns associated with delivery systems utilizing viral vectors or nanoparticles have not been adequately resolved. Therefore, optimizing the BBB penetrability and cell-targeted delivery systems for STING inhibitors, and developing small molecules or nanocarriers capable of efficiently crossing the BBB, represent research directions of significant clinical application value. In summary, despite the core challenges of drug delivery efficiency, safety, and disease heterogeneity that still need to be overcome, research in this field offers novel perspectives for treating neurodegenerative diseases. With the convergence of precision medicine, nanotechnology, gene editing, and other disciplines, therapies targeting the cGAS-STING pathway hold promise for providing a new therapeutic paradigm for neurodegenerative diseases—encompassing prevention, delaying pathological progression, and functional restoration.

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n.a.

Authors' contributions
H.L: Conceptualization, Literature search, Data curation, Writing - Original Draft, Visualization.R.C: Literature search, Methodology, Writing - Review & Editing.Y.Z: Validation, Writing - Review & Editing, Supervision.Y.J: Validation, Writing - Review & Editing, Supervision.S.T: Conceptualization, Writing - Review & Editing, Supervision, Project administration.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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