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REVIEW

Mitophagy and cGAS−STING crosstalk in neuroinflammation

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Neurodegenerative diseases

Abstract Mitophagy, essential for mitochondrial health, selectively degrades damaged mitochondria. It is intricately linked to the cGAS−STING pathway, which is crucial for innate immunity. This pathway responds to mitochondrial DNA and is associated with cellular stress response. Our review explores the molecular details and regulatory mechanisms of mitophagy and the cGAS−STING pathway. We critically evaluate the literature demonstrating how dysfunctional mitophagy leads to neuroinflammatory conditions, primarily through the accumulation of damaged mitochondria, which activates the cGAS−STING pathway. This activation prompts the production of pro-inflammatory cytokines, exacerbating neuroinflammation. This review emphasizes the interaction between mitophagy and the cGAS−STING pathways. Effective mitophagy may suppress the cGAS−STING pathway, offering protection against neuroinflammation. Conversely, impaired mitophagy may activate the cGAS−STING pathway, leading to chronic neuroinflammation. Additionally, we explored how this interaction influences neurodegenerative disorders, suggesting a common mechanism underlying these diseases. In conclusion, there is a need for additional targeted research to unravel the complexities of mitophagy−cGAS−STING interactions and their role in neurodegeneration. This review highlights potential therapies targeting these pathways,

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potentially leading to new treatments for neuroinflammatory and neurodegenerative conditions. This synthesis enhances our understanding of the cellular and molecular foundations of neuroinflammation and opens new therapeutic avenues for neurodegenerative disease research.

1. Introduction

Neuroinflammation, which encapsulates intricate immune responses within the central nervous system (CNS), has increasingly become a focal point of research in neurodegenerative diseases[1]. This multifaceted phenomenon, characterized by the activation of resident glial cells, the release of numerous pro-inflammatory cytokines, and the recruitment of peripheral immune cells to the CNS, represents a double-edged sword for neuronal health[2,3]. Historically, the CNS was considered an immunologically privileged site, shielded from the peripheral immune system by the blood−brain barrier (BBB)[4,5]. Recently, the prevailing view of the relationship between the CNS and the immune system has evolved, largely due to accumulating evidence highlighting their intricate interactions[6]. Acute neuroinflammation is typically regarded as a beneficial mechanism that aids in eliminating pathogens, compromised cells, and cellular debris[7,8]. However, chronic inflammation frequently leads to deleterious outcomes[9]. Prolonged neuroinflammation has been implicated in exacerbating neuronal injury, driving the progression of diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS)[9−12].

An immediate inquiry that surfaces is as follows: What orchestrates the balance between the beneficial and harmful aspects of neuroinflammation? Upon delving into the molecular mechanisms involved, mitophagy and the cyclic GMP−AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway are identified as principal agents in this process[13]. Mitophagy, a specific type of autophagy, targets and removes damaged mitochondria to preserve cellular balance and prevent inflammation[14,15]. Conversely, the cGAS−STING pathway acts as a sentinel of innate immunity and is primed to detect and respond to cytosolic DNA, notably mitochondrial DNA (mtDNA), which might escape during instances of compromised mitophagy[16,17]. Activation of this pathway can initiate a cascade of inflammatory responses, having profound implications for the CNS[17,18]. The convergence of these two processes in the context of neuroinflammation offers rich insight into molecular interactions, feedback loops, and regulatory checkpoints[13,19]. Their crosstalk provides insights into the cellular and molecular dynamics underpinning the neuroinflammatory responses observed in various neurodegenerative conditions[19]. Moreover, understanding this interplay holds the promise of unveiling novel therapeutic targets, potentially reshaping the landscape of treatment strategies for a range of neurological disorders[19,20].

This review embarks on a journey to explore the research surrounding autophagy/mitophagy and the cGAS−STING pathway, as well as their intricate relationships since 1957 (Fig. 1). It integrates current knowledge, challenges existing paradigms, and charts the course for future investigations. By thoroughly analyzing the molecular dynamics, cellular implications, and wider physiological effects, we aim to offer a detailed overview of the crosstalk between mitophagy and the cGAS−STING pathway, emphasizing its crucial role in influencing neuroinflammatory responses. Considering the aforementioned factors, researchers must explore these molecular pathways in great detail, as they not only offer insights into the pathogenesis of neurodegenerative diseases but also pave the way for innovative therapeutic interventions.

2. The key role of mitophagy in neuroinflammation

Mitophagy is a specialized form of autophagy that specifically targets mitochondria, the powerhouses of the cell, for degradation and recycling. This selective process is essential for maintaining cellular health and function by ensuring that damaged or dysfunctional mitochondria are efficiently removed. This process is critical because mitochondria are responsible for producing the energy needed by cells. Malfunctioning mitochondria can lead to a wide range of cellular problems, including impaired energy metabolism, increased oxidative stress, and activation of apoptotic pathways. The importance of mitophagy extends beyond cellular energy metabolism; it plays a key role in modulating responses to cellular stress, regulating cell signaling, and influencing cell survival and death, development, differentiation, aging, and immune function. This underscores its vital role in maintaining cellular integrity and preventing disease. The significance of mitophagy is further highlighted through its association with a range of health conditions, encompassing neurodegenerative diseases, cardiovascular disorders, cancer, metabolic disorders, aging, immune disorders, and muscular disorders[21,22] (Fig. 2). In the context of neuroinflammation, mitophagy has emerged as a key regulator of maintaining neuronal and glial cell health. It prevents the accumulation of damaged mitochondria, a critical factor that can amplify inflammatory responses and accelerate the progression of neurodegenerative diseases[23]. When mitochondria become damaged, they can release pro-inflammatory molecules and reactive oxygen species (ROS), exacerbating neuroinflammation[24]. This inflammation can in turn cause further damage to mitochondria, creating a vicious cycle[25]. Dysregulated mitophagy, therefore, plays a role in the progression of various neurodegenerative diseases, such as PD, AD, and ALS[26−28]. Targeting and improving mitophagy might offer therapeutic potential for these neuroinflammatory conditions.

2.1. *Fundamentals and biological relevance of mitophagy*

Mitochondria are double membrane organelles responsible for generating adenosine triphosphate (ATP), the primary energy currency of the cell[29]. This is achieved through oxidative phosphorylation, a process that harnesses energy from electron transport chains located within mitochondrial membranes[30]. In addition to energy production, mitochondria are intricately involved in other vital cellular processes, including calcium regulation, lipid metabolism, and apoptosis (programmed cell death)[15,31]. Given these multifaceted roles, it becomes evident that maintain-

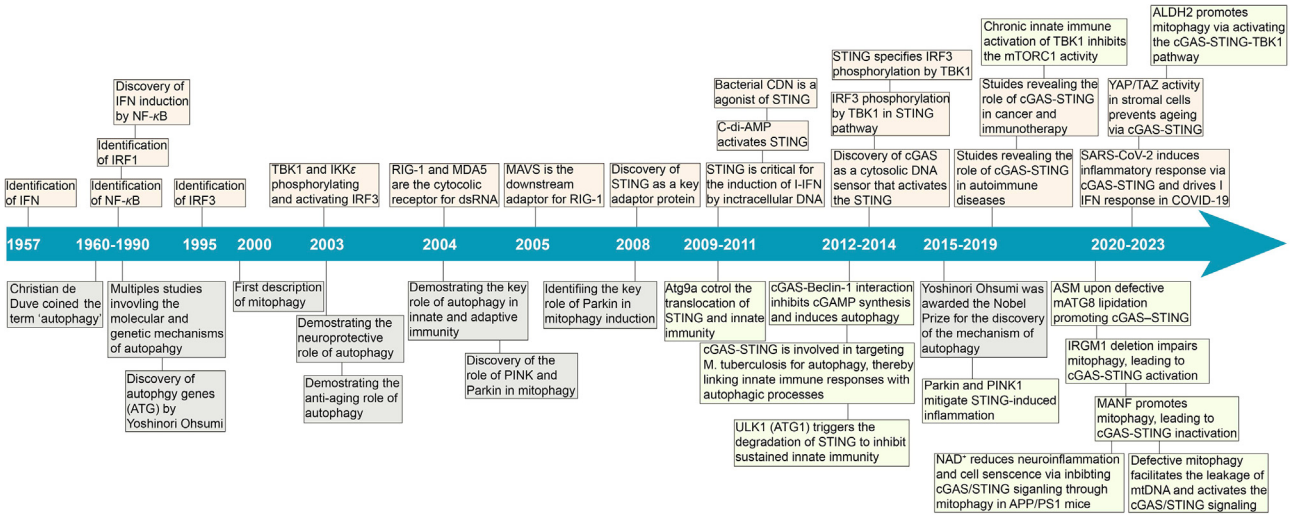

Figure 1 This timeline depicts a selection of significant discoveries related to autophagy/mitophagy (light brown), cGAS−STING (light yellow), and their interactions (light green). Regarding the research on autophagy, Christian de Duve first coined the term 'autophagy' in 1963, leading to a series of crucial discoveries. These include the complex pathways of autophagy/mitophagy, ranging from simple yeast organisms to animals such as mice. In 2016, Yoshinori Ohsumi was rightfully awarded the Nobel Prize in Physiology or Medicine for his pioneering work in the field of autophagy, underscoring the importance of this area of research. In the study of cGAS−STING, notable discoveries include the identification of key proteins such as IFN, NF-κB, and IRF3; the recognition of STING as a crucial adaptor protein for intracellular DNA-induced IFN response; and the discovery of cGAS as a cytosolic DNA sensor activating STING. Over the past decade, there has been an increasing focus on the interplay between autophagy/mitophagy and cGAS−STING. This includes research on the regulatory effect of cGAS−STING on the induction of autophagy/mitophagy and the inhibitory impact of autophagy/mitophagy on the activation of cGAS−STING and subsequent immune responses.

ing mitochondrial health and function is crucial for the overall well-being of the cell[32]. The necessity for mitophagy arises from the inherent susceptibility of mitochondria to damage[33]. Over time, these organelles can become compromised due to various factors, including the production of ROS, mtDNA mutations, and exposure to certain environmental stressors[34,35]. Damaged mitochondria not only are less efficient at maintaining their primary functions but can also become detrimental to the cell, producing harmful byproducts, and exacerbating cellular stress[36,37]. Once a damaged or dysfunctional mitochondrion is identified in a cell, mitophagy is initiated[38]. The targeted mitochondrion is enveloped by a phagophore, a double-membraned structure that expands to engulf the organelle. This process results in the maturation of autophagosomes, which subsequently fuse with lysosomes. Within this combined structure, termed an autolysosome, the mitochondrial contents are degraded by lysosomal enzymes, and the resulting macromolecules are recycled back into the cytosol for reuse[39].

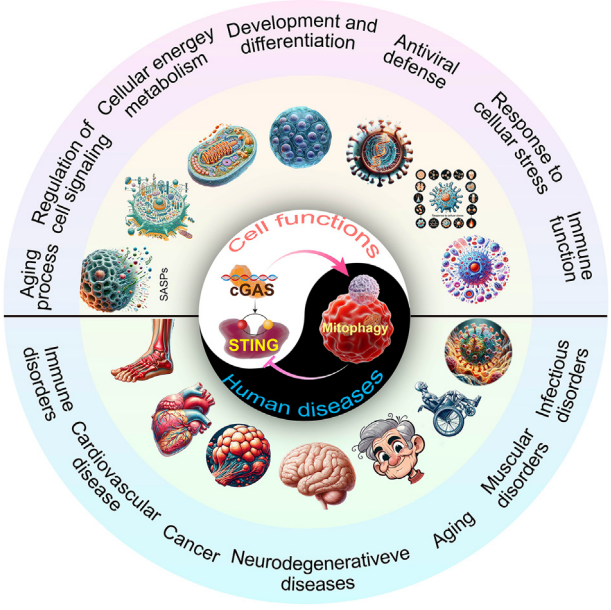

Figure 2 The cellular functions of mitophagy and the c-GAS−STING pathway and their implications in various human diseases.

The biological relevance of mitophagy extends beyond the cellular level, impacting tissue function, organ health, and overall organismal well-being[40]. Mitophagy plays a protective role, especially in tissues with high metabolic demands, such as the heart and brain[41,42]. By ensuring the removal of dysfunctional mitochondria, mitophagy prevents the accumulation of harmful byproducts that can lead to cellular damage and death. Furthermore, by recycling mitochondrial components, mitophagy supports cellular energy demands and metabolic processes. Dysregulation of mitophagy has been implicated in a myriad of diseases[34,43,44]. For instance, in neurodegenerative diseases such as PD and AD, impaired mitophagy leads to the accumulation of damaged mitochondria in neurons, contributing to neuronal death and disease progression[43−45]. Similarly, in cardiac diseases, compromised mitophagy can exacerbate cardiac injury and dysfunction[46,47]. Moreover, the role of mitophagy in aging has garnered increased attention, with evidence suggesting that enhanced mitophagy can promote longevity and mitigate age-associated pathologies[48].

In essence, mitophagy is a critical biological process with wide-reaching implications for maintaining cellular and organismal health. Its protective role against cellular damage and its association with various diseases underscores the importance of

further research. Understanding the detailed mechanisms and potential therapeutic applications of mitophagy is crucial for developing strategies to prevent and treat diseases, highlighting the need for comprehensive studies on its regulatory pathways and interactions.

2.2. *Mechanisms of mitophagy initiation and progression*

The molecular mechanisms underlying the initiation and progression of mitophagy are intricate and involve a series of proteins and pathways that ensure the targeted degradation of damaged or superfluous mitochondria[49]. Notably, two core molecular players pivotal for mitophagy activation, PTEN-induced kinase 1 (PINK1) and Parkin are involved in this process[35]. Under normal physiological conditions, mitochondria function optimally to maintain their membrane potential. PINK1, a protein that is encoded by the Parkinson disease 2 gene in humans and mice, is continuously imported into healthy mitochondria, specifically targeting the inner mitochondrial membrane where it is rapidly degraded by mitochondrial proteases, ensuring that its intracellular levels remain low[50]. This continuous import and degradation cycle acts as a surveillance mechanism, ensuring that only functional mitochondria persist. Nevertheless, upon mitochondrial impairment or diminished membrane potential, PINK1 import is arrested, prompting PINK1 accumulation on the outer mitochondrial membrane (OMM) and effectively flagging the mitochondrion as malfunctioning[39]. Rather than mere passive accumulation, PINK1 actively ushers on Parkin, an E3 ubiquitin ligase, from its customary cytosolic location to malfunctioning mitochondria[36,51]. PINK1 directly phosphorylates Parkin, an action that catalyzes the ligase function of Parkin[35]. Once localized on the OMM in its activated form, Parkin embarks on its primary task, ubiquitinating an array of OMM-associated proteins[38]. This ubiquitination process effectively "tags" or "labels" the damaged mitochondrion, marking it for eventual degradation[50]. Following the ubiquitination of mitochondrial proteins by Parkin, autophagy receptors, including optineurin (OPTN), nuclear dot protein 52 kDa, voltage-dependent anion channel 1, and p62/SQSTM1, are recruited[35,51–53]. These receptors recognize and bind to ubiquitinated proteins, facilitating the formation of the phagophore, a double-membrane structure that begins to envelop the targeted mitochondria. The expansion of the phagophore is facilitated by various autophagy-related genes, which ensure the elongation and closure of the phagophore, leading to the complete encapsulation of the damaged mitochondrion within an autophagosome[36]. Additionally, PINK1 has another pivotal function: phosphorylating both Parkin and the ubiquitin moieties that Parkin attaches to OMM proteins[35]. This phosphorylation of ubiquitin further enhances Parkin activity *via* a positive feedback loop, ensuring a robust and amplified response to mitochondrial damage[38]. The ubiquitinated proteins on the OMM are products of the enzymatic activity of Parkin and then serve as signals or beacons for the recruitment of downstream autophagy machinery, setting the stage for engulfment of the damaged mitochondrion and its eventual degradation within the lysosome[50]. This intricate and coordinated interaction between PINK1 and Parkin ensures that cells can efficiently and selectively identify, target, and remove mitochondria that are no longer functional or that pose a potential threat to cellular health[51]. The importance of the PINK1−Parkin pathway is underscored by the fact that mutations in the genes encoding these proteins are linked to familial forms of PD, underscoring its imperative role in mitochondrial regulation and broader human health paradigms[54–56].

While the PINK1/Parkin pathway is a well-characterized mechanism for mitophagy initiation, several other pathways and molecular players have emerged as significant contributors to this process[49,57]. Parkinson disease (autosomal recessive, early onset) 7 (PARK7, also known as DJ-1) is another protein implicated in PD[57]. Recent studies have highlighted its role in PINK1/Parkin-mediated mitophagy[38]. Although DJ-1 is not a direct initiator of mitophagy, it acts as an essential downstream mediator[57]. In the context of mitochondrial damage, DJ-1 translocates to depolarized mitochondria in proximity to autophagy receptors such as OPTN[57]. This translocation is dependent on PINK1 and Parkin but does not require oxidation of the cysteine residue of DJ-1[57]. Interestingly, without PINK1 signaling-mediated mitochondrial damage or Parkin-mediated ubiquitination, overexpressed DJ-1 cannot effectively initiate the tagging and recognition steps necessary for mitophagy, despite its protective role against mitochondrial dysfunction[57]. DJ-1 cannot compensate for the loss of PINK1 kinase activity and Parkin E3 ubiquitin ligase activity, which occur upstream of this pathway, underscoring the importance of a comprehensive approach to understanding and treating PD. By focusing on both the unique and collective functions of these proteins, researchers are laying the foundation for innovative therapies that could offer hope to millions of people worldwide affected by PD. In the context of diabetic nephropathy, characterized by kidney damage due to diabetes, the Src protein has been identified as a regulator of mitophagy. Src activation aggravates podocyte injury in diabetic nephropathy by suppressing the FUN14 domain containing 1 (FUNDC1)-mediated mitophagy[58]. FUNDC1, a mitochondrial outer membrane protein, acts as a receptor for mitophagy, especially under hypoxic conditions. The interplay between Src and FUNDC1 highlights the role of non-canonical pathways in disease-specific contexts[59]. Triple-negative breast cancer is a aggressive form of breast cancer. Recent findings show that mitochondrial uncoupling protein 1 (UCP1) negatively regulates triple-negative breast cancer progression[60]. UCP1 overexpression not only induces mitochondrial swelling but also activates mitophagy[60]. Furthermore, UCP1 overexpression activate gasdermin E, a core protein involved in pyroptosis, a form of inflammatory cell death[60]. This study underscores the interconnectedness of mitophagy, mitochondrial dynamics, and other forms of cell death in the context of cancer[60]. Although not directly related to mitophagy, the emerging role of non-canonical Wnt signaling in cardiovascular diseases is worth noting[61]. This pathway has been linked to key mechanisms of atherosclerosis, including oxidative stress and endothelial dysfunction[62–64]. Targeting components of non-canonical Wnt signaling pathways offers potential therapeutic avenues for treating cardiovascular diseases. While the PINK1/Parkin pathway is central to our understanding of mitophagy, it is clear that a myriad of other proteins and pathways also play crucial roles in this process (Fig. 3). These alternative pathways not only expand our understanding of mitophagy but also offer potential therapeutic targets for a range of diseases. The intricate nature of these pathways and their interplay in various disease contexts underscore the need for holistic therapeutic strategies. Understanding the nuances of these mechanisms allow us to better tailor interventions

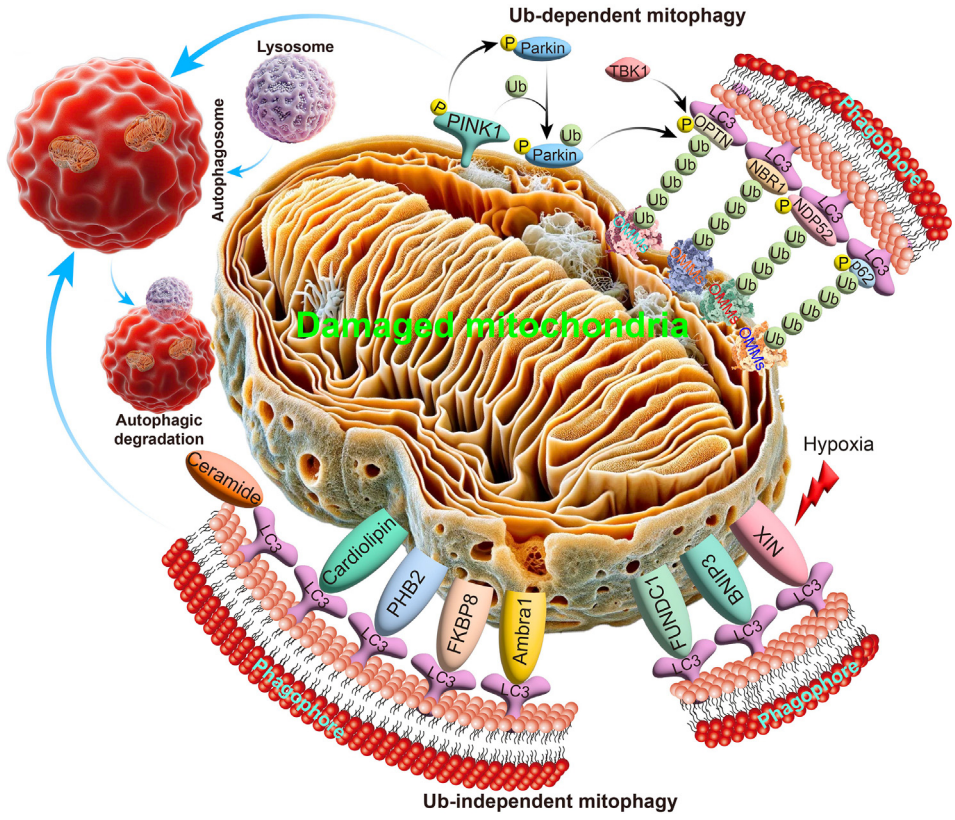

Figure 3 The molecular mechanisms of mitophagy. The diagram illustrates two classical mitophagy pathways: the ubiquitin-dependent pathway and the ubiquitin-independent pathway. In the ubiquitin-dependent pathway, when mitochondria are stressed, PINK1 is stabilized on the OMM and activated through autophosphorylation. It then phosphorylates Parkin and ubiquitin, enhancing Parkin's E3 ligase activity. This results in the ubiquitination of several OMM proteins, which results in the formation of polyubiquitin chains that PINK1 further phosphorylates, creating a self-amplifying loop. These chains attract adaptor proteins such as OPTN, nuclear dot protein 52 kDa (NDP52), NBR1, and p62, which bind to LC3, initiating autophagosome formation. The binding of OPTN to ubiquitin chains is further strengthened by TBK1-mediated phosphorylation. In the ubiquitin-independent pathway, under hypoxic conditions, proteins such as FUNDC1, BNIP3, and NIX play crucial roles in recruiting autophagosomes to mitochondria through their interaction with LC3. During mitophagy, Ambra1 is instrumental in relocating HUWE1 from the cytosol to the mitochondria, leading to the degradation of mitofusin 2, a necessary step for Ambra1-driven mitophagy. Additionally, the IκB kinase α phosphorylates S1014 on *Ambra1*, enabling its interaction with LC3. PHB2, an inner mitochondrial membrane protein, is key for directing mitochondria toward autophagic degradation. The externalization of cardiolipin (CL) to the OMM in response to mitochondrial damage acts as a signal for the selective autophagic removal of dysfunctional mitochondria, with CL interacting with LC3 in mammalian cortical neurons. Ceramide serves as a selective mitophagy receptor by directly binding to LC3, as does FKBP8, an OMM protein, promoting the degradation of damaged mitochondria through interactions with LC3.

to specific disease states, potentially offering more effective and targeted treatments.

2.3. *Implications of mitophagy for neuroinflammation*

Neuroinflammation, characterized by the activation of glial cells and the release of pro-inflammatory cytokines, plays a central role in the pathology of many neurodegenerative diseases[65]. Disruption of mitophagy, leading to the accumulation of damaged mitochondria, exacerbates this condition by producing ROS. These ROS not only further damage cellular components, contributing to the pathological features observed in diseases such as AD and PD[66−68], but also release mitochondrial components that activate microglia. This activation can induce a chronic inflammatory state in the brain, impairing neuronal function and accelerating the progression of neurodegenerative diseases[69,70].

Recent studies underscore the linkage between impaired mitophagy/autophagy and elevated neuroinflammation across a broad range of neurological disorders, such as Huntington's disease (HD), ALS, ischemia/reperfusion (I/R), chronic cerebral ischemia (CCI), and multiple sclerosis (MS), as evidenced by cellular, animal, and clinical research (Table 1). This connection is especially pronounced in AD, where mitochondrial dysfunction, ineffective mitophagy/autophagy, and increased pro-inflammatory responses are observed in both patient brains and *in vitro* and *in vivo* disease models[71−73]. Critical autophagy genes, such as Beclin-1, PINK1, and autophagy-related gene 5 (*Atg5*), play essential roles in regulating microglial activation and, consequently, neuroinflammation[71,74,75]. The potential of mitophagy/autophagy induction to counteract these pathological processes is supported by findings that inducers such as urolithin A (UA) and actinonin (AC) can significantly reduce pro-inflammatory cytokine levels [*e.g.*, interleukin 6 (IL-6) and tumor

Table 1 The implications of mitophagy/autophagy defects or activation in triggering or inhibiting neuroinflammation.

Type of diseases	Cell, animal, and human sample	The evidence of mitophagy/autophagy in neuroinflammation	Molecular mechanism
AD[73]	BV-2 cells; primary microglia from mice and postmortem human AD brains	Genetic reduction of Beclin-1 impairs microglial phagocytosis	Beclin 1-mediated autophagy
AD[74]	LPS/ATP-stimulated primary microglia from Beclin-$1^{+/-}$ and Beclin-$1^{+/-}$ APP/PS1 mice	Beclin-$1^{+/-}$ and Beclin-$1^{+/-}$ APPPS1 mouse microglia exhibit activation of the NLRP3 inflammasome	CALCOCO2-mediated autophagy
AD[94]	fAβ-treated primary microglia	si*Map1lc3B* and si*Atg7* aggravates the activation of the NLRP3 inflammasome in fAβ-treated microglia	AMPK-mediated autophagy
AD[75]	$MnCl_2$ $4H_2O$ + LPS-induced mice and BV-2 cells	The hippocampus of mice and BV2 cells exhibit activation of the NLRP3 inflammasome and autophagy dysfunction	*Atg5*-dependent autophagy
AD[71]	Primary microglia; APP/PS1 mice	Depletion of PINK1 increases the expression of TNF-α in microglia; UA or AC reduces L-6 and TNF-α levels and increases IL-10 levels in APP/PS1 mice; UA inhibits the NLRP3 inflammasome in APP/PS1 mice	PINK1/Parkin-mediated mitophagy
AD[76]	APP/PS1 mice	UMI-77 reduces IL-6 and TNF-α levels in APP/PS1 mice	MCL-1-mediated mitophagy
AD[23]	Aβ_{42}-induced BV2; APP/PS1 mice	PSS inhibits the activation of the NLRP3 inflammasome in Aβ_{42}-induced BV2 and APP/PS1 mice	SHP-2-mediated mitophagy
AD[81,82]	Aβ_{1-42}-treated primary astrocyte from Sprague−Dawley rats	Aβ induces autophagy dysfunction and inflammatory responses in astrocytes; Progesterone induces autophagy and inhibits the NLRP3 inflammasome	mTOR-mediated autophagy
PD[84]	α-Synuclein A53T-*Tg* mice; SN4741 cells; BV-2 cells	α-synuclein A53T-*Tg* mice exhibits activation of the NLRP3 inflammasome and chaperone-mediated autophagy impairment	p38−TFEB-mediated autophagy
PD[86]	MPTP-induced mice; LPS-induced BV-2	Deletion or knockdown of *Atg5* in microglia exacerbates MPTP- or LPS-induced activation of the NLRP3 inflammasome	*Atg5*-dependent autophagy
PD[85]	Primary microglia from α-synuclein A53T-*Tg* mice; α-synuclein A53T-*Tg* mice	α-Synuclein induces microglial autophagic impairment; Depletion of *Atg5* in microglia exacerbates the neuroinflammation in α-synuclein A53T-*Tg* mice	TLR4 and its downstream p38 and Akt−mTOR-mediated autophagy
PD[87]	*Atg5* WT and *Atg5* cKO mice	Deletion or knockdown of *Atg5* in microglia induces the activation of the NLRP3 inflammasome	*Atg5*-dependent autophagy
PD[88]	LPS/MPP^+-induced N9 cells; MPTP-induced mice	LPS/MPP^+ impairs the initial step of autophagosome formation; andrographolide inhibits the NLRP3 inflammasome	PINK1/Parkin-mediated mitophagy
Depression; PD[91]	LPS/ATP-induced BV2 and primary microglia; LPS-treated mice	LPS/ATP-induced BV2 cells and LPS-treated mice exhibit impaired autophagy flux and inhibition of the PINK1/Parkin pathway; QU inhibits the NLRP3 inflammasome	PINK1/Parkin-mediated mitophagy
PD[83]	MPTP-induced mice	MPTP induces mitochondrial damage, ROS generation, and the activation of the NLRP3 inflammasome; Rapa rescues astrocytic Kir6.1 deletion-induced neuroinflammation	PINK1/Parkin-mediated mitophagy
PD[89]	MPTP-induced mice; LPS-induced BV-2 cells	MPTP induces autophagic flux and neuroinflammation; UA inhibits the NLRP3 inflammasome	PINK1/Parkin-mediated mitophagy
PD[23]	A53T α-synuclein overexpressing BV2 cells	PSS inhibits the NLRP3 inflammasome	SHP-2-mediated mitophagy
PD[90]	α-Synuclein A53T-*Tg* mice; MPTP-induced mice; LPS-induced mice; LPS/ATP-induced primary microglia and BV-2 cells	PD mice and LPS/ATP-induced microglia exhibit activation of the NLRP3 inflammasome; KPF inhibits the NLRP3 inflammasome	*Atg5*-dependent autophagy
HD[95]	zQ175 neo-deleted knockin mice; HD hESC-derived striatal cells; HD-homo, HD-het, and control cells	The inflammatory response and autophagic flux are increased	cGAS−STING-dependent pathway

Table 1 (*continued*)

Type of diseases	Cell, animal, and human sample	The evidence of mitophagy/autophagy in neuroinflammation	Molecular mechanism
HD[23]	mHTT74 overexpressing BV2 cells	PSS inhibits the NLRP3 inflammasome	SHP-2-mediated mitophagy
ALS[96]	LPS-stimulated *C9orf72*-ALS iPSC-derived microglia	mC9-MG exhibits a deficit of the autophagy initiation and activation of the NLRP3 inflammasome and NF-κB signaling	C9ORF72-mediated autophagy
ALS[97]	$SOD1^{G93A}$ mice	Increased microtubule-associated protein 1 light chain 3 beta, p62, Ub, microgliosis, and the activation of the NLRP3 inflammasome can be found in the anterodorsal thalamic nucleus	−
MS[98]	LPS-induced BV-2 cells; MOG35-55-treated mice	AXL induces autophagy to mitigate inflammatory responses	PI3K/AKT/mTOR-mediated autophagy
MS[99]	LPS-induced BV-2 cells; MOG35-55-treated mice	α7nAChR induces autophagy to mitigate spinal inflammatory responses	AMPK−mTOR−p70S6K-mediated autophagy
MS[100]	LPS-induced BV-2 cells; MOG35-55-treated mice	CB2R induces autophagy and inhibits the NLRP3 inflammasome	*Atg5*-dependent autophagy
CCI[101]	BCCAo rats	BCCAo rats exhibit microglial overactivation and activation of the NLRP3 inflammasome; Blocked autophagy and mitophagy flux aggravate the activation of the NLRP3 inflammasome; URB597 induces mitophagy and inhibits the NLRP3 inflammasome	−
I/R[102]	MCAO rats	MCAO rats exhibit activation of the NLRP3 inflammasome and autophagic dysfunction; RVT inhibits the NLRP3 inflammasome	Sirt1−AMPK-mediated mitophagy
I/R[103]	MCAO rats	GSK-3β knockdown and SB216763 inhibits the NLRP3 inflammasome	GSK-3β-mediated autophagy
Depression[104]	Chronic unpredictable mild stress-induced mice	Andrographolide inhibits inflammation and blocks the assembly of NLRP3	−
Early brain injury[105]	Subarachnoid hemorrhage rats	MT inhibits the NLRP3 inflammasome	PINK1/Parkin-mediated mitophagy

Aβ, amyloid beta; AC, actinonin; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; *Atg5*, autophagy-related gene 5; ATP, adenosine triphosphate; *C9orf72*, chromosome 9 open reading frame 72; CCI, chronic cerebral ischemic; HD, Huntington's disease; I/R, ischemia/reperfusion; KPF, kaempferol; LPS, lipopolysaccharide; MCAO, middle cerebral artery occlusion; MOG, myelin oligodendrocyte glycoprotein; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; NF-κB, nuclear factor-kappa B; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; Rapa, rapamycin; PD, Parkinson's disease; PSS, *Polygala* saponins; QU, quercetin; RVT, resveratrol; ROS, reactive oxygen species; TNF-α, tumor necrosis factor alpha; UA, urolithin A; WT, wild-type.

necrosis factor-alpha (TNF-α)] and inhibit the activation of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, a crucial component of the neuroinflammatory response[71]. Similarly, other inducers, including UMI-77, metformin, and NAD^+, have shown effectiveness in AD models, offering promise for therapeutic intervention[76−80]. In addition to these inducers, natural compounds such as *Polygala* saponins (PSS) and progesterone have been shown to mitigate NLRP3 inflammasome activation and neuroinflammation through mitophagy/autophagy induction, suggesting a holistic approach for managing these complex pathways[23,81,82]. This approach is particularly relevant for PD research, where mitochondrial damage, elevated ROS levels, and NLRP3 inflammasome activation have been documented[83,84]. The essential role of autophagy genes in maintaining neuronal health is highlighted by the exacerbation of neuroinflammation and disruption of mitophagy/autophagy flux following their deletion or knockdown, such as with *Atg5*[85−87]. Conversely, mitophagy/autophagy inducers not only reduce neuroinflammation but also enhance neuronal viability and ameliorate PD-like behaviors[23,83,88−91].

Given the pivotal role of mitophagy in maintaining mitochondrial health and its implications for neuroinflammation, enhancing mitophagy presents a promising therapeutic strategy for neurodegenerative diseases[92]. Drugs that stimulate mitophagy or prevent the accumulation of damaged mitochondria could reduce neuroinflammation and decelerate disease progression[23,93]. Furthermore, elucidating the intricate relationship between mitophagy and neuroinflammation can pave the way for personalized medicine, with treatments are administered based on individual mitophagy and inflammatory profiles. As research in this area advances, developing targeted interventions that modulate mitophagy offers hope for individuals affected by neurodegenerative conditions, highlighting the importance of continued investigation into these mechanisms.

3. cGAS−STING pathway: A central player in neuroinflammation

The cGAS−STING pathway is a crucial part of the immune response. The proteins cGAS and STING, essential in the cGAS−STING pathway, have distinct structural features crucial for their function. cGAS, with its unique two-domain structure, including a nucleotidyltransferase domain and a DNA-binding domain, is activated upon binding to cytosolic DNA, leading to

cyclic GMP−AMP (cGAMP) synthesis. STING, a transmembrane protein with a key C-terminal domain, binds to cGAMP, triggering a conformational change that activates downstream immune responses. These structural characteristics are central to the ability of these proteins to detect cytosolic DNA and initiate immune defense mechanisms. The cGAS−STING pathway is integral to a spectrum of cellular functions, playing pivotal roles in innate immunity, antiviral defense, the response to DNA damage, autophagy, the regulation of inflammation, cellular aging, tumor surveillance, and the modulation of interferon signaling (Fig. 2). This pathway is relevant for various pathological conditions. Notably, its dysregulation is implicated in the pathogenesis of autoimmune and inflammatory diseases and is often triggered by aberrant activation in response to self-DNA, culminating in persistent inflammation. In the realm of oncology, the cGAS−STING pathway plays a dichotomous role: it contributes to tumor suppression through the initiation of immune responses against neoplastic cells, while paradoxically, it may also facilitate tumor progression and survival in certain contexts. A comprehensive understanding of this pathway is thus imperative for the development of novel therapeutic strategies targeting a broad spectrum of diseases, including infectious diseases, autoimmune disorders, cancers, aging, and aging-related diseases[106,107] (Fig. 2). Recent insights underscored the importance of the cGAS−STING pathway in neurodegenerative diseases, where it has emerged as a key player in the mediation of neuroinflammation[108]. Intriguingly, while this pathway is essential for defending against pathogens, overactivation or dysregulation of this pathway can lead to detrimental effects in the CNS[109,110]. To appreciate its significance in neuroinflammation, understanding its role in innate immunity, activation mechanisms, and specific implications for neuroinflammation is essential[111,112]. Recent studies highlight the dual role of the cGAS−STING pathway in the CNS, where it can act as a protective mechanism against genuine threats but can also exacerbate neuroinflammatory responses under certain conditions[111,112]. The cGAS−STING pathway, central to innate immunity, has profound implications for neuroinflammation[110]. Its activation within the CNS can be a double-edged sword, offering protection against genuine threats but also contributing to neuroinflammatory and neurodegenerative pathologies[111,113]. As research continues to unravel the complexities of this pathway within the brain, it offers both challenges and opportunities for therapeutic interventions in a range of neurological conditions[111]. The potential to modulate this pathway for therapeutic benefit is an exciting frontier in neuroimmunology research. Understanding its precise role and regulation will be pivotal for harnessing its potential benefits while mitigating its risks.

3.1. *Role of cGAS−STING in innate immunity*

Innate immunity, often referred to as the body's natural defense system, is characterized by rapid and nonspecific responses to potential threats[114]. In contrast to adaptive immunity, which is slower but more specific, immune evasion relies on memories generated from previous encounters with pathogens[114]. At the heart of the innate immune system's ability to detect and respond to a myriad of challenges is the cGAS−STING pathway, a sophisticated signaling cascade that has emerged as a central player in the defense against microbial invaders and cellular aberrations[115,116].

The cell is equipped with numerous sensors designed to detect various forms of threats. These sensors, known as pattern recognition receptors, recognize pathogen-associated molecular patterns and damage-associated molecular patterns[117]. Among these pattern recognition receptors, cGAS is unique because of its ability to sense aberrant DNA in the cytoplasm[113]. This specificity of cGAS in detecting aberrant DNA has underscored its evolutionary significance in cellular defense. Under physiological conditions, DNA is restricted to the nucleus and mitochondria. However, during instances of cellular stress, microbial invasion, or DNA damage, DNA fragments can escape these compartments and enter the cytoplasm[118]. cGAS, strategically positioned in the cytosol, recognizes and binds to this misplaced DNA[119]. Its binding is not sequence-specific, allowing it to detect a wide range of DNA structures, from viral genomes to mtDNA fragments[120]. Upon binding to dsDNA, cGAS activates its enzymatic function, leading to the synthesis of cGAMP from ATP and GTP[121,122]. This molecule is not just a byproduct of cGAS's enzymatic activity; it is also a potent alarm signal[123]. cGAMP acts as a secondary messenger, alerting the cell to the presence of foreign or misplaced DNA and setting the stage for a coordinated immune response[124]. STING, which resides dormant on the endoplasmic reticulum (ER), initiates its action upon encountering cGAMP[125]. The binding of cGAMP induces a series of structural and functional changes in STING, allowing it to transition from the ER to other cellular compartments[126]. This dynamic movement of STING is a test of the cell's ability to rapidly respond to threats[127]. This movement is strategic, facilitating the recruitment and activation of various signaling molecules essential for mounting an immune response[120]. Once activated, STING orchestrates a series of signaling events, recruiting and activating kinases, which in turn activate transcription factors[128]. These events culminate in the production of type I interferons (IFNs), especially interferon-beta (IFN-β), and a range of pro-inflammatory cytokines[17,129]. These molecules serve multiple purposes: they establish an antiviral state within the cell, recruit and activate other immune cells, and alert neighboring cells to potential threats, ensuring a coordinated and robust defense mechanism[108]. While the cGAS−STING pathway is a cornerstone of innate immunity, its effects ripple into the realm of adaptive immunity. Activation of the cGAS−STING pathway induces pro-inflammatory cytokine secretion, pivotal for the activation of macrophages and T cells, illustrating how innate immunity modulates adaptive immunity[17,130,131]. This modulation bridges the gap between the immediate, nonspecific response of innate immunity and the slower, more targeted response of adaptive immunity, ensuring comprehensive defense against threats.

In conclusion, the cGAS−STING pathway highlights the evolutionary sophistication of cellular defenses, bridging the detection of aberrant DNA to a robust immune response. This phenomenon underscores the complexity and adaptability of the innate immune system, which responds swiftly to diverse challenges. This pathway's role in orchestrating an immediate defense while facilitating communication with adaptive immunity ensures a comprehensive and coordinated response to pathogens and cellular abnormalities. Understanding this pathway will enrich our understanding of the intricacies of the immune system and its capacity for precision in safeguarding cellular integrity.

3.2. *Activation mechanisms and downstream signaling pathways of cGAS−STING*

The cGAS−STING pathway functions as a sentinel of cellular integrity, monitoring the cytosolic environment for the presence of aberrant DNA. Its activation triggers a cascade of events that not

only neutralize immediate threats but also prepare the cell and its neighbors for potential challenges. The intricate steps involved in the activation of this pathway and the subsequent signaling events are examples of the cell's evolutionary refinement in orchestrating a precise and coordinated immune response.

Under normal circumstances, the cell cytoplasm is devoid of DNA. However, during microbial invasion, cellular damage, or certain pathological conditions, DNA can enter the cytosol[132]. cGAS recognizes this DNA and binds to it regardless of its sequence[133]. This binding is not a passive event; it induces a significant conformational change in cGAS, activating its enzymatic domain[133]. This activation sets the stage for the synthesis of the secondary messenger, cGAMP[134]. Notably, the evolutionary conservation of this mechanism from bacteria to animals underscores its fundamental importance in cellular defense. cGAMP is not merely a byproduct of cGAS's interaction with DNA; it is a potent molecular signal that heralds the presence of potential threats within the cell[135]. As a secondary messenger, cGAMP's primary role is to relay the alarm to STING, the primary responder in this signaling cascade. In its inactive state, STING resides on the ER membrane. The binding of cGAMP to STING induces a series of structural rearrangements in STING, allowing it to form homodimers. These dimers then transition from the ER to the Golgi apparatus and subsequently to perinuclear endosomes[17]. This translocation facilitates the recruitment and activation of various signaling molecules essential for mounting an immune response[136]. The precision of these molecular events speaks to the cell's ability to respond to threats rapidly and effectively. One of the first molecules to be recruited by STING is TANK-binding kinase 1 (TBK1)[137]. This kinase plays a pivotal role in translating STING's activation into a transcriptional response[138]. Once activated by STING, TBK1 targets the transcription factor interferon regulatory factor 3 (IRF3). The phosphorylation of IRF3 by TBK1 induces its dimerization and prepares it for nuclear translocation[139]. Upon dimerization, IRF3 translocates to the nucleus. Within this compartment, it binds to specific DNA sequences, promoting the transcription of type I interferon (IFN) genes. These genes, particularly IFN-β, are instrumental in establishing an antiviral state within the cell, preparing it for potential viral challenges[140]. While IRF3 activation and nuclear translocation are significant events, the cGAS−STING pathway also concurrently activates another powerful signaling cascade involving nuclear factor-kappa B (NF-κB)[129]. Once activated, this transcription factor promotes the production of numerous pro-inflammatory cytokines[126,129]. These cytokines amplify the immune response, ensuring a comprehensive defense mechanism that not only neutralizes threats but also alerts neighboring cells to potential dangers[141,142]. Given the potency of the cGAS−STING response, the pathway incorporates several feedback loops and regulatory mechanisms[143,144]. These steps ensure the response is proportional to the threat and that the pathway returns to its resting state once the threat is neutralized. Therefore, this regulation is crucial for preventing excessive inflammation or potential autoimmunity.

In summary, the cGAS−STING pathway is crucial for detecting DNA anomalies and triggering immune responses, revealing the evolutionary sophistication of the immune system. It combines detection, signaling, and regulatory mechanisms to protect against threats while maintaining cellular balance (Fig. 4). The conservation of this pathway across species underscores its fundamental role in immunity. Its potential for therapeutic applications in treating infections, autoimmune diseases, and cancer highlights its medical significance. Understanding cGAS−STING signaling is key to enhancing the immune system's capacity to balance defense and homeostasis.

3.3. *Implications of cGAS−STING for neuroinflammation*

The CNS is a complex and delicately balanced environment crucial for maintaining neurological function, where the balance between protective and pathological processes is essential[145]. Within this context, the cGAS−STING pathway has emerged as a significant player that influences both protective outcomes and pathological conditions[111]. This pathway plays a dual role in defending against external threats while also being implicated in various neuroinflammatory conditions, highlighting its multifaceted role in CNS health and disease[111] (Table 2).

In the field of AD, the cGAS−STING pathway has been identified as a pivotal mechanism contributing to the neuroinflammatory processes underlying disease pathogenesis, with significant implications for both understanding AD and identifying potential therapeutic targets. Studies have shown that activation of this pathway in the brains of AD patients plays a crucial role in the progression of this disease, including cognitive impairment and amyloid beta (Aβ) pathology[146], suggesting that targeting this pathway could provide a novel therapeutic strategy for AD[147]. Further research has revealed specific mechanisms through which tau proteins, a hallmark of AD, activate microglia and induce neuroinflammation *via* the cGAS−STING pathway. This discovery points to a shared inflammatory pathway between neurodegenerative diseases and viral infections, further emphasizing the pathway' significance in CNS disorders[148]. Investigations into the downstream effects of the cGAS−STING pathway, particularly its role in activating type I IFNs and driving neuroinflammation and synapse loss in AD, highlight the critical role of IFN signaling in the neuropathogenic processes associated with AD, linking the cGAS−STING pathway to synaptic dysfunction and neurodegeneration[149]. Additionally, evidence suggests that Aβ peptides, which are central to AD pathology, trigger neuroinflammation and microglial activation *via* the cGAS−STING pathway, adding another layer to our understanding of the pathway's role in the inflammatory response to AD pathology[150]. The interplay between viral infections and AD risk has also been explored, revealing that certain viral infections downregulate triggering receptor expressed on myeloid cells 2 (TREM2) in microglia through the cGAS−STING pathway. TREM2 is a protein linked to AD risk, and this discovery suggests complex relationships between viral infections, innate immune responses, and AD pathogenesis, highlighting the therapeutic potential of targeting this pathway[151]. The cGAS−STING pathway is also crucial in PD, particularly due to its role in mitochondrial dysfunction and neuroinflammation. Mutations in Parkin and PINK1, which are associated with early-onset PD, lead to mitochondrial stress and activation of the STING pathway, causing inflammation and dopaminergic neuron loss. However, research has shown that mitigating STING activity through genetic deletion or pharmacological inhibition can rescue these detrimental effects, suggesting a protective mechanism against PD progression[19]. Further studies have demonstrated the activation of this pathway in models of α-synucleinopathy, in which α-synuclein aggregates increase STING expression and activation, leading to neurodegeneration. Notably, STING-deficient mice exhibit protection from neuron loss, highlighting the potential of this pathway as a therapeutic target in PD and

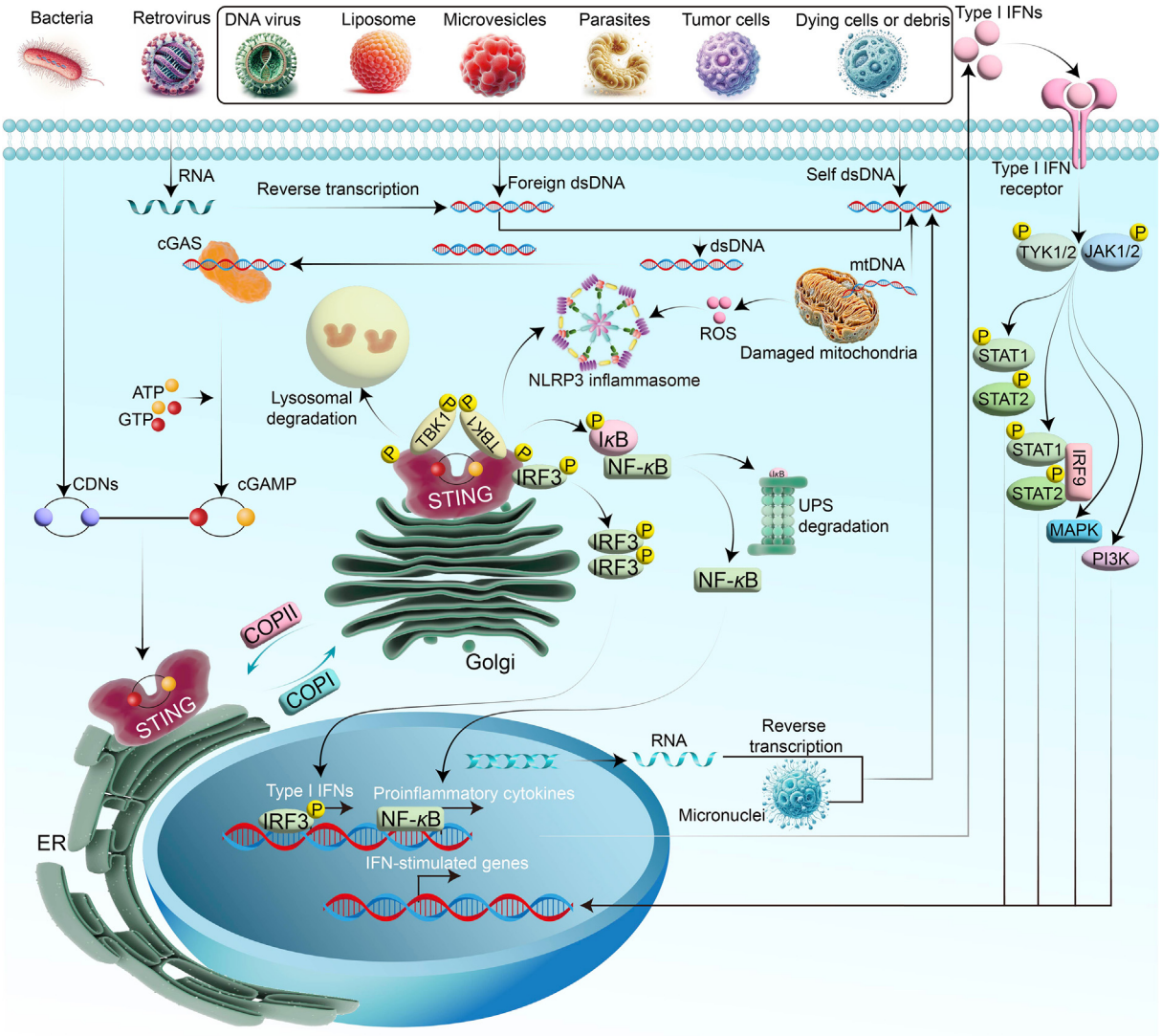

Figure 4 DNA sensing and signaling in the cGAS−STING pathway. This pathway leads to the production of type I IFNs and inflammatory cytokines. Abnormal DNA in the cytoplasm, originating from either pathogen infection (bacteria, DNA viruses, or retroviruses) or cellular damage, activates this process. cGAS binds to double-stranded DNA (dsDNA) and becomes active, converting ATP and GTP into 2′,3′-cGAMP. This compound subsequently activates the adaptor protein STING. STING, upon binding to cGAMP, changes conformation and moves from the ER to the Golgi. In the Golgi, STING attracts TBK1, which phosphorylates the C-terminal tail of STING. This phosphorylated STING recruits IFN regulatory factor 3 (IRF3), which TBK1 also phosphorylates and activates. The activated IRF3 dimer travels to the nucleus, where it regulates type 1 IFN transcription and triggers type I IFN responses. Secreted IFN-β, through its receptor, activates TYK and JAK signals, influencing the STAT, MAPK, and PI3K pathways. This enhances IFN-stimulated gene transcription *via* a positive feedback loop. Concurrently, the cGAS−STING pathway activates NF-κB signaling, regulating inflammatory cytokine gene transcription. The NLRP3 inflammasome, which is triggered by increased ROS, is further upregulated by the STING protein. Additionally, STING initiates autophagy for degradation.

related disorders[152]. Additionally, the role of the pathway has been confirmed is underscored in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse models of PD, in which cGAS deficiency in microglia controls neuroinflammation and neurotoxicity. This finding suggested that targeting microglial cGAS could be a therapeutic strategy, as evidenced by the neuroprotection conferred by cGAS inhibitors during MPTP exposure[153]. Chronic activation of STING, as shown in models expressing a constitutively active variant, leads to dopaminergic neuron degeneration, pathological α-synuclein, and neuroinflammation. This finding indicates that prolonged STING activation is detrimental and that preventing such inflammatory responses may offer therapeutic benefits for PD and other neurodegenerative diseases[154]. In ALS, the cGAS−STING pathway is a critical mediator of the neuroinflammatory processes that exacerbate disease progression. Research has illuminated how this pathway is activated in ALS through various mechanisms. The accumulation of TAR DNA-binding protein 43 (TDP-43), a protein that is a hallmark of ALS, triggers the release of mtDNA *via* the mitochondrial permeability transition pore, activating the cGAS−STING pathway and leading to inflammation[155]. Additionally, the loss of chromosome 9 open reading frame 72 (*C9orf72*), a gene associated with familial ALS, in myeloid cells results in hyperactivation of STING and an elevated type I IFN response, further contributing to inflammation[156]. Moreover, in models of ALS

Table 2 The implications of the cGAS−STING pathway in neuroinflammation.

Type of diseases	Cell, animal, and human sample	The evidence of cGAS−STING in neuroinflammation
AD[147]	Primary microglia, neurons, and astrocytes; aged and 5xFAD mice; the prefrontal cortex of human AD	Elevated p-STING, p-TBK1, p-p65, and p-IRF3 levels were observed in the cortex of human AD, aged, and 5xFAD mice; $cGAS^{-/-}$ reduces Aβ pathology, neuroinflammation, and cognitive decline in 5xFAD mice; $cGAS^{-/-}$ also prevents astrocytes from becoming harmful A1 types, reducing Aβ peptide-induced neuronal damage
PD[19]	*Parkin*$^{-/-}$, *Pink1*$^{-/-}$, *Sting*$^{-/-}$, and *Lrrk2* G2019S mice	*Parkin*$^{-/-}$ mice accumulate mutations in mtDNA; $STING^{-/-}$ entirely stops inflammation from intense exercise or mtDNA mutation and lessens dopaminergic neuron loss and motor issues in *Parkin*$^{-/-}$ and *Pink1*$^{-/-}$ mice
Aging[163]	Primary microglia and BV2; aged mice	STING activation leads to neurodegeneration and cognitive decline by causing reactive microglial states; mtDNA release in aging brains activates cGAS in microglia, inducing age-related transcriptional changes that result in inflammation, neurotoxicity, and memory impairment
ALS[155]	iPSC-derived motor neurons; TDP-43 mutant mice; spinal cord samples from ALS patients	The deletion of cGAS and STING stops NF-κB and type I IFN increase caused by TDP-43 in motor neurons and TDP-43 mutant mice; ALS patients have higher cGAMP levels in their spinal cords
ALS/FTD[156]	*C9orf72*$^{-/-}$ myeloid cells; *C9orf72*$^{-/-}$ mice	C9orf72$^{-/-}$ myeloid cells are selectively hyperresponsive to STING activators; STING inhibition reduces overactive type I IFN responses in *C9orf72*$^{-/-}$ myeloid cells and lessens splenomegaly and inflammation in *C9orf72*$^{-/-}$ mice
HD[95]	hESC-derived neuron, cGASΔ in HD-homo cells; the brain tissue of HD patients	*Cgas* mRNA shows high ribosome activity at exon 1 and specific pauses at codons 171 and 172 in HD striatal cells; cGAS protein levels and activity, as well as *Ccl5* and *Cxcl10* expression, are higher in HD striatum; cGAS depletion reduces its activity and lowers inflammatory gene expression in HD cells
Chronic neurodegeneration[164]	*Ifnar1*$^{-/-}$ and Sting$^{-/-}$ mice	STING-dependent IFN activates microglia and promotes the neurodegenerative progression
I/R[159]	MCAO mice	Brain ischemia causes dsDNA release into the cytosol, triggering inflammation through cGAS activation
Macular degeneration[165]	Human RPE cells; *Ifnar1*$^{-/-}$, *Stat2*$^{-/-}$, *Mb21d1*$^{-/-}$, and *Ppif*$^{-/-}$ mice	cGAS triggers IFN-β in RPE degeneration in human cells and mice; lowering DICER1 or Alu RNA buildup causes mtDNA to enter the cytosol and activate cGAS
Traumatic brain injury[166]	WT and *Sting*$^{-/-}$ mice	STING contributes to harmful neuroinflammation after traumatic brain injury, as shown by higher levels of TNF-α, IL-6, IL-1β, and IFNs
HSE[167]	Primary neurons, microglia, and astrocytes; WT, *Sting*$^{-/-}$, and *Cgas*$^{-/-}$ mice	HSV triggers IFN in brain microglia *via* cGAS−STING; Mice lacking cGAS or STING are more prone to acute HSE, with increased viral replication in neurons of *Sting*$^{-/-}$ mice. HSV-infected microglia activate STING-dependent antiviral responses in neurons and stimulate IFN production in astrocytes through toll-like receptor 3
CVST[168]	Ferric chloride-induced male C57BL/6J mice	cGAS and STING increase significantly in mouse brain microglia after CVST, which releases dsDNA into the cytoplasm, causing inflammation through the cGAS−STING pathway
AD, HD[148]	Primary microglia; R6/2 and *Pqbp1*-cKO mice	Polyglutamine binding protein 1 senses extrinsic tau 3R/4R proteins by direct interaction and triggers an innate immune response by activating the cGAS−STING pathway
Neuropathic pain[169]	BV-2; SNI-induced rats	SNI detects external tau 3R/4R proteins through direct interaction, initiating an immune response by activating the cGAS−STING pathway
Metabolic syndrome-associated cognitive impairment[170]	*Cgas*$^{-/-}$ mice	HFD leads to microglial activation, particularly in female *Cgas*$^{-/-}$ mice
AD[171]	Loxp (*Cgas* fl/fl; *Cx3cr1*$^{-/-}$), mKO (*Cgas* fl/fl; *Cx3cr1*$^{+/-}$), 5xFAD (5xFAD; *Cgas* fl/fl; *Cx3cr1*$^{-/-}$), and 5xFAD mKO (5xFAD; *Cgas* fl/fl; *Cx3cr1*$^{-/-}$) mice; postmortem human brain and spinal cord sample	Microglia primarily cause the increase in cGAS−STING signaling; Removing cGAS from microglia at the start of Aβ pathology greatly reduces plaque formation and protects against Aβ-induced cognitive decline; cGAS is essential for plaque-related microglial increase and for developing the DAM

(*continued on next page*)

Table 2 (*continued*)

Type of diseases	Cell, animal, and human sample	The evidence of cGAS−STING in neuroinflammation
		phenotype; Loss of microglial cGAS lowers dystrophic neurites, thus preserving synaptic and neuronal function
PD[152]	Primary microglia, astrocyte, and neurons; αSyn-PFF injected and *Sting*$^{-/-}$ mice; SNpc tissue from autopsied idiopathic PD patients	The cGAS−STING pathway is activated before neurodegeneration begins, leading to type-I interferon activation; *Sting*$^{-/-}$ mice are protected from loss of dopaminergic neurons; In PD SNpc tissues, STING levels closely match the amount of pS129-αSyn; αSyn aggregates elevate STING expression and enhance its activation
AD[149]	APPNL-G-F, 5XFAD, APP; tTa, and APP/PS1 mice, rIFN-β- and generic NA-containing amyloid fibrils-treated WT mice; Mixed glia and hippocampal slice cultures	Activation of the IFN pathway occurs in the brains of various AD mouse models, WT mice exposed to amyloid fibrils, and the brains of deceased AD patients; IFN triggers microglial activation and synapse loss in 5XFAD mice
AD[150]	BV2	cGAS−STING-IFITM3 axis may be involved in Aβ-induced neuroinflammation in microglia
MS[158]	WT and *Sting*$^{-/-}$ mice with EAE	EAE induction significantly boosts STING expression in Iba1+ myeloid cells and Tmem119+ microglia; *Sting*$^{-/-}$ mice show less severe EAE development compared to WT mice
Acute viral encephalitis[172]	Vero cells, BV2, and iPSC-derived microglia; WT, *Sting*$^{-/-}$, *Cgas*$^{-/-}$, rf3$^{-/-}$, *Irf3s1/s1*, and *Ifnar*$^{-/-}$ mice	Microglia and immune cells die *via* apoptosis in HSV-infected brains through the cGAS−STING pathway, independent of Type I IFN signaling
I/R[160]	BV2 and HEK293T cells; *Cgas* cKO, *Hdac3* cKO, and *Cx3cr1*$^{CreER\text{-}IRES\text{-}EYFP}$ mice	mtDNA activates microglial cGAS−STING, leading to pro-inflammatory conditions; The deletion of cGAS or HDAC3 reduces I/R-induced neuroinflammation and brain damage
PD[154]	WT, *Sting* N153S/WT ki, *Sting* ki, *Ifnar1*$^{-/-}$, and *Casp1*$^{-/-}$ mice	Chronic activation of the STING pathway leads to dopaminergic neuron degeneration
I/R[162]	BV2; WT and *Sting*$^{-/-}$ mice	STING expression increased in microglia following MCAO; STING deletion alleviates brain infarction, neuronal damage, and neurobehavioral issues in MCAO mice, also decreasing microglial activation and inflammatory chemokines, and lessening microglial pyroptosis
PD[153]	MPTP-induced WT and *Cgas*$^{-/-}$ mice	cGAS−STING pathway activation in MPTP mice causes neuroinflammation; Microglial cGAS deficiency reduces this inflammation and toxicity
Post-infection AD[151]	human induced pluripotent stem cells derived microglia	TREM2 enhances virus-induced IFN-β production *via* the cGAS−STING pathway in microglia, boosting STING signaling and TBK1 and IRF3 activation
ALS[157]	Immortalized human microglia, microglia, oligodendrocyte lineage cells, neurons, and astrocytes; WT, SOD1^{G93A}, SOD1^{G85R}, and STING/G93A double-positive mice	ALS-causing misfolded SOD1 leads to mitochondrial damage, releasing mtDNA and RNA:DNA hybrids into the cytosol, activating type I IFN and related genes *via* IRF3 and IFNAR, independent of mPTP; cGAS/DDX41-STING signaling is amplified in neighboring cells through gap junctions
I/R[161]	WT, *Sting*$^{-/-}$, *Cgas*$^{-/-}$, and *Nlrx1*$^{-/-}$ mice	*Sting* and *Ifn* genes are increased after CCI injury; The loss of cGAS or STING reduced inflammation and conferred neuroprotection at 24 h, with *Cgas*−/− mice showing fewer motor deficits after 4 days and less tissue damage after 14 days

Aβ, amyloid beta; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; *C9orf72*, chromosome 9 open reading frame 72; CCI, cranial cervical instability; CVST, cerebral venous sinus thrombosis; DAM, disease-associated microglia; EAE, experimental autoimmune encephalomyelitis; FTD, frontotemporal dementia; HD, Huntington's disease; HDAC3, histone deacetylase 3; HFD, high fat diet; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; IFN, interferon; IFNs, interferons; iPSC, induced pluripotent stem cells; I/R, ischemia/reperfusion; MCAO, middle cerebral artery occlusion; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; PD, Parkinson's disease; RPE, retinal pigmented epithelium; SNI, spared nerve injury; SOD1, superoxide dismutase type 1; TDP-43, TAR DNA-binding protein 43; TREM2, triggering receptor expressed on myeloid cells 2; WT, wild-type.

associated with SOD1 mutations, mitochondrial damage leads to the release of mtDNA and RNA:DNA hybrids, activating the cGAS−STING pathway. This activation not only triggers an inflammatory response but also allows this response to spread to neighboring cells, amplifying the neuroinflammation observed in ALS[157]. Furthermore, in other CNS disorders, such as HD, the cGAS pathway plays a crucial role in regulating inflammation and autophagy, as indicated by increased cGAS activity and expression of inflammatory genes in the HD striatum. Depletion of cGAS reduces inflammation and autophagy, while its restoration in HD cells promotes these responses[95]. In a mouse model of MS, the induction of experimental autoimmune encephalomyelitis (EAE) significantly increased the expression of STING in myeloid cells marked by *Iba1*$^{+}$ and microglia marked by *Tmem119*$^{+}$. However, compared with wild-type (WT) mice, mice lacking STING (STING$^{-/-}$) experience less severe development of EAE. The antiviral drug ganciclovir induces a

type I IFN response in microglia through the STING pathway, thereby reducing microglial reactivity and neuroinflammation[158]. In the context of stroke, brain ischemia leads to the release of dsDNA and mtDNA, activating the cGAS−STING pathway and triggering inflammation. The deletion of cGAS or STING reduces inflammation and provides neuroprotection in various models of brain injury, including I/R injury and CCI injury[159−162].

Overall, the cGAS−STING pathway has emerged as a central mediator of neuroinflammation across a spectrum of CNS disorders, underscoring its potential as a therapeutic target. By modulating this pathway, it may be possible to alleviate the inflammatory responses that contribute to the progression of neurodegenerative diseases, offering hope for new treatments that can slow or halt the course of these debilitating conditions.

The brain, while shielded by the BBB, is not impervious to viral infections. Viruses such as herpes simplex virus (HSV) and Zika can invade the CNS, leading to neuroinflammation and potential neurological deficits[173,174]. Upon viral invasion, the release of viral DNA into the cytoplasm of CNS-resident cells can activate the cGAS−STING pathway[175]. This activation triggers the production of type I IFNs and pro-inflammatory cytokines, establishing an antiviral state within the cell[175]. This response not only is crucial for inhibiting viral replication but also acts as a beacon, signaling other immune cells to the site of infection, thereby amplifying the defense mechanism[175]. In addition to the immediate antiviral response, the cGAS−STING pathway also facilitates communication between infected and uninfected cells[143]. The cytokines and chemokines produced as a result of pathway activation can recruit immune cells to the site of infection, bolstering the defense of the CNS against viral threats[176,177]. MS is an autoimmune condition in which the body's immune system mistakenly attacks the myelin sheath of neurons[178]. Recent research has suggested that the cGAS−STING pathway might play a role in the pathogenesis of MS[179]. Activation of this pathway in CNS-resident cells can amplify the inflammatory response, leading to enhanced demyelination and worsening of clinical symptoms[179].

Given the dual role of the cGAS−STING pathway in the CNS, there are both challenges and opportunities for therapeutic intervention[111]. It is imperative to strike a balance when targeting this pathway, ensuring that while its pathological implications are mitigated, its protective roles are not compromised. Targeting this pathway could lead to novel strategies for treating viral infections of the CNS, neurodegenerative conditions, and autoimmune disorders. However, any therapeutic approach must consider the pathway's protective role, ensuring that interventions do not compromise the CNS's ability to defend against genuine threats. As research progresses, the cGAS−STING pathway represents a promising target for developing treatments for various neurological diseases, underscoring the importance of understanding its dual role in the CNS.

4. Molecular crosstalk: Mitophagy and cGAS−STING

The intricate interplay between cellular processes ensures the maintenance of homeostasis and appropriate response to stressors[180]. Within the realm of neuroinflammation, the crosstalk between mitophagy and the cGAS−STING pathway has garnered significant attention[181,182]. Recent studies have highlighted the importance of this crosstalk in the context of neurodegenerative diseases, where dysregulation of either pathway can exacerbate disease progression[19]. This molecular dialog underscores the complexity of cellular responses and offers insights into the pathogenesis of various neuroinflammatory conditions. Notably, the balance between these pathways is delicate, and any disruption can lead to exacerbated inflammatory responses or compromised cellular health. The molecular interaction between mitophagy and the cGAS−STING pathway provides insight into the intricacies of cellular defense mechanisms and homeostasis. Their crosstalk, especially within the CNS, has profound implications for neuroinflammation and the pathogenesis of various neurological conditions[183]. As our understanding of this molecular crosstalk has improved, potential therapeutic targets for a range of inflammatory and degenerative conditions have been identified.

4.1. *Dysfunctional mitophagy and the release of mtDNA*

Mitophagy is essential for cellular health, especially in high-demand environments like neurons[184]. Interestingly, the importance of mitophagy in neurons is further emphasized by the fact that neurons are postmitotic cells, meaning that they do not divide. This makes the efficient removal of damaged mitochondria even more crucial[181]. This process is regulated by molecular signals, and proteins such as PINK1 and Parkin label damaged mitochondria for autophagic degradation. This mechanism ensures the efficient elimination of dysfunctional mitochondria, balancing mitochondrial fission and fusion to optimize function and prevent damage accumulation[33]. Compared with nuclear DNA, mtDNA is more exposed and lacks protective histones, increasing susceptibility to damage from ROS generated during cellular respiration[185]. When mitochondria are damaged, there is not only a risk of compromised energy production but also the danger of mtDNA release into the cytoplasm[186]. In the cytosol, mtDNA, due to its bacterial-like characteristics, can be mistaken for a foreign entity, potentially activating various innate immune pathways, including the cGAS−STING axis[183,187]. Moreover, mitophagy protects cellular health by rapidly removing damaged mitochondria, preventing mtDNA leakage into the cytosol, and thus avoiding immune activation[188,189]. This containment is crucial for preventing unwanted immune activation and maintaining cellular homeostasis. However, mitophagy is not infallible. Genetic mutations, as observed in certain hereditary forms of PD, can impair mitophagy[190,191]. Environmental toxins, oxidative stress, and the natural aging process can also challenge the efficiency of mitophagy[40,192]. When mitophagy is compromised, damaged mitochondria accumulate, increasing the risk of mtDNA release and the subsequent activation of inflammatory pathways[193]. Importantly, while mitophagy is a protective mechanism, mitophagy dysfunction can be a double-edged sword, leading to both energy deficits and inflammatory responses[194]. Effective mitophagy is crucial, particularly in neurons, to prevent mitochondrial dysfunction and its consequences. Focusing on the role of mitophagy in health and disease, it has become clear that its regulation is key to preventing neurodegenerative and inflammatory conditions[195]. Enhancing our understanding and targeting of mitophagy propose new therapeutic options for these disorders, marking an important area for future research. This perspective underscores the need for balanced cellular mechanisms and the potential of mitophagy-focused therapies for treating neurological diseases.

4.2. *cGAS−STING activation by mtDNA: Implications for neuroinflammation*

The inadvertent presence of mtDNA in the cytoplasm potently triggers innate immune responses[196]. This activation, particularly

through the cGAS−STING axis, has profound implications for cellular health, especially within the delicate environment of the CNS[197]. Understanding the cascade of events following mtDNA escape and subsequent activation of the cGAS−STING pathway provides insights into the pathogenesis of various neuroinflammatory and neurodegenerative conditions[110]. mtDNA, a relic of the organelle's bacterial ancestry, is distinct from nuclear DNA. Its circular configuration, certain unmethylated CpG motifs, and other unique features make it structurally similar to bacterial DNA[198]. While safely housed within the mitochondria, mtDNA is harmless. However, once the fungus finds its way into the cytoplasm, the cell perceives it as a danger signal, akin to an invading pathogen's DNA[196]. Once in the cytoplasm, mtDNA can bind to and activate cGAS, leading to the synthesis of cGAMP. This secondary messenger subsequently activates STING, initiating a signaling cascade that culminates in the production of type I IFNs and pro-inflammatory cytokines[17].

The CNS is a delicate and intricately balanced environment in which neurons and glial cells work in harmony to ensure proper brain function. However, disruptions in this process, especially those stemming from chronic activation of immune pathways such as the cGAS−STING axis, can have profound and often detrimental consequences[199]. Emerging evidence indicates the importance of sustained cGAS−STING activation within the CNS[200]. Microglia, often termed the "sentinels" of the brain, are on constant alert for signs of injury, infection, or other disturbances. Under physiological conditions, microglia exist in a quiescent state, surveying their environment and supporting neuronal function. However, activation of the cGAS−STING pathway can shift microglia from the resting state to the pro-inflammatory phenotype[199]. In this state, they release numerous pro-inflammatory cytokines, such as interleukin 1 beta (IL-1β), TNF-α, and IL-6, which can perpetuate inflammation and disrupt neuronal homeostasis[201]. Astrocytes, another major glial cell type, can also become reactive in the face of chronic neuroinflammation[202]. Reactive astrocytes can produce and release inflammatory mediators, further amplifying the inflammatory response initiated by microglia[203]. Moreover, their ability to regulate neurotransmitter levels and maintain the extracellular environment can be compromised, affecting neuronal signaling[203,204]. Chronic neuroinflammation can lead to alterations in synaptic function[205]. Inflammatory mediators can modulate neurotransmitter release, receptor expression, and synaptic plasticity[206,207]. Over time, these disruptions can impair learning, memory, and other cognitive functions[208,209]. Moreover, neurons, especially those in certain vulnerable regions such as the hippocampus and substantia nigra, can become targets of inflammatory responses[210,211]. Chronic exposure to inflammatory mediators can induce oxidative stress, mitochondrial dysfunction, and even apoptotic cell death in these neurons[196]. The balance of excitatory and inhibitory neurotransmission is crucial for proper brain function[212]. Chronic inflammation can disrupt this balance, potentially leading to conditions such as excitotoxicity, where excessive glutamate signaling can damage or kill neurons[213]. The BBB is composed of specialized endothelial cells connected by tight junctions[214]. Chronic inflammation can induce stress in these cells, leading to the expression of adhesion molecules and the recruitment of peripheral immune cells[215]. Once the integrity of the BBB is compromised, peripheral immune cells, including T cells, B cells, and monocytes, can infiltrate the brain[216]. These cells can release their own set of inflammatory mediators, exacerbating the already heightened state of neuroinflammation[216]. A compromised BBB can also allow potentially neurotoxic substances, including pathogens, toxins, and metabolic waste products, to enter the CNS, posing additional threats to neuronal health[217].

Chronic activation of the cGAS−STING pathway has been implicated in the pathogenesis of AD[147]. Sustained neuroinflammation can exacerbate Aβ deposition and tau hyperphosphorylation, hallmark features of AD[38,171,200,218]. Furthermore, inflammation can impair synaptic function and neuronal viability in regions critical for memory, such as the hippocampus[171]. In PD, dopaminergic neurons in the substantia nigra are particularly vulnerable. Chronic neuroinflammation, driven by cGAS−STING activation, can exacerbate oxidative stress in these neurons, accelerating their degeneration and leading to the motor symptoms characteristic of PD[197,219]. MS is an autoimmune condition in which the myelin sheath of neurons is attacked. Chronic activation of the cGAS−STING pathway can amplify the inflammatory response in MS, leading to enhanced demyelination and neurodegeneration[199,220]. Thus, complex neurons in the CNS and the glial network are acutely sensitive to disruptions in homeostasis. Chronic activation of the cGAS−STING pathway leads to neuroinflammation, which adversely affects neuronal health, synaptic function, and overall brain integrity[196]. Insight into this pathway within the CNS context illuminates promising therapeutic strategies aimed at reducing neuroinflammation and safeguarding neurological function, identifying a crucial area for future research to explore and develop targeted interventions.

4.3. *The regulatory effect of cGAS−STING on mitophagy*

The regulation of autophagy/mitophagy by the cGAS−STING pathway is a critical aspect of cellular homeostasis and the immune response. This intricate regulatory mechanism plays a pivotal role in how cells respond to DNA damage, infection, and other stressors[221]. Activation of the cGAS−STING pathway marks the beginning of a complex signaling cascade that triggers an immune response and significantly influences mitochondrial dynamics and mitophagy, creating a feedback loop that can either amplify or dampen cellular responses[13]. This feedback mechanism is crucial for maintaining cellular homeostasis, particularly under conditions of stress or damage. The trafficking of STING is a critical step in its activation, regulated by various proteins and posttranslational modifications[222]. For instance, inhibiting ADP-ribosylation factor GTPases, which are involved in vesicular trafficking, can block STING activation, underscoring the importance of its proper localization within the cell[223]. Palmitoylation, a type of post-translational modification, at specific cysteine residues in the Golgi apparatus is also crucial for STING activation. This modification enhances the interaction of STING with its downstream effectors, facilitating the immune signaling cascade[224]. Once STING has fulfilled its signaling role, it is rapidly targeted for degradation to prevent overactivation of the immune response. This degradation likely occurs through autophagy[225]. Mitochondrial fission is crucial for removing damaged portions of mitochondria and facilitating their degradation *via* mitophagy[226]. Recent studies show that STING activation can upregulate proteins such as dynamin-related protein 1 (DRP1), a key player in mitochondrial fission[227]. Enhanced fission, while beneficial in some contexts, can lead to mitochondrial fragmentation if not regulated[227]. Mitochondrial fusion allows for the merging of two mitochondria, a process that can dilute damage

and share mitochondrial contents[226]. STING activation downregulates fusion proteins such as mitofusin 1 and mitofusin 2, potentially inhibiting the fusion process[134,228−230]. Reduced fusion can isolate damaged mitochondria, preventing them from merging with healthier counterparts[231]. Additionally, the autophagy kinase unc-51 like autophagy activating kinase 1 (ULK1) is implicated in targeting STING for degradation, although the precise underlying mechanisms remain to be fully elucidated[232,233]. Depending on the context, this can promote or inhibit the initiation of the autophagic process. Microtubule-associated protein 1 light chain 3 beta and p62/SQSTM1 are critical for autophagosome formation and cargo recognition[184]. Activation of the cGAS−STING pathway can modulate the levels and activity of these proteins, influencing the efficiency of autophagosome

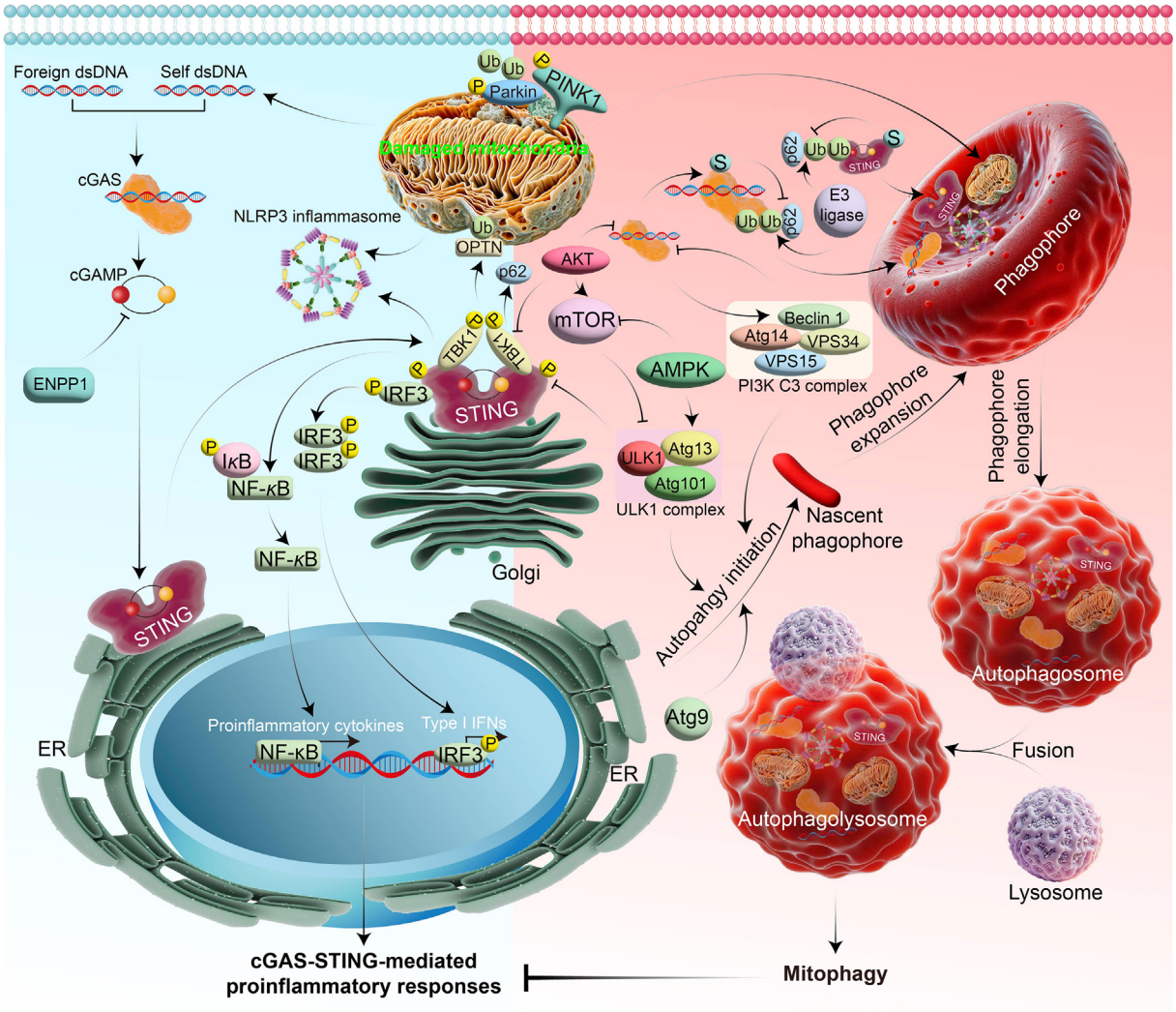

Figure 5 Crosstalk between the regulatory mechanism of autophagy/mitophagy and cGAS−STING. The cGAS−STING pathway is a crucial mechanism in the innate immune system and is primarily responsible for detecting cytoplasmic DNA, which is indicative of either pathogenic infection or cellular damage. When cGAS encounters this DNA, it becomes activated and synthesizes the messenger molecule cGAMP. This molecule then binds to STING, a protein on the ER, triggering its conformational change and relocation to the Golgi apparatus. STING activates a cascade of immune responses, primarily through the activation of TBK1 and subsequent phosphorylation of IRF3 and NF-κB activation, leading to the production of type I IFNs and inflammatory cytokines. Autophagy and mitophagy are sophisticated cellular processes for maintaining cellular homeostasis. Autophagy is activated by nutrient deprivation or other stressors, in turn engaging the ULK1 complex and the Beclin-1 complex, which are modulated by the balance of AKT and AMPK signaling. The ULK1 complex initiates autophagy, while the Beclin-1 complex nucleates the formation of autophagosomes. Mitophagy, a specialized form of autophagy that targets mitochondria, is primarily regulated by the PINK1/Parkin pathway. PINK1 accumulates on damaged mitochondria, where it recruits Parkin, which ubiquitinates mitochondrial proteins, signaling for autophagic degradation. Proteins such as p62 are involved in recognizing ubiquitinated proteins and facilitating mitophagy. Intriguingly, the cGAS−STING pathway intersects with these autophagic processes. cGAS and STING can undergo autophagic degradation mediated by p62, which recognizes ubiquitinated forms of these proteins. Beclin-1, an essential component of the autophagy initiation complex, can both inhibit and be activated by cGAS, indicating a complex regulatory interaction. Furthermore, ULK1 can inhibit the phosphorylation of STING, which is crucial for its activation, and attenuate the activity of cGAS. In this intricate network, TBK1 further enhances the ubiquitination of OPTN, another autophagy-related protein, adding another layer of regulation. This interplay between the autophagy/mitophagy pathway and the cGAS−STING pathway highlights the complexity of cellular responses to stress and infection, revealing potential therapeutic targets for diseases involving these pathways.

formation and subsequent mitophagy[184]. The final step of mitophagy involves the fusion of autophagosomes with lysosomes, leading to the degradation of their contents. The cGAS−STING pathway can influence lysosomal pH and enzyme activity, potentially affecting the degradation efficiency of mitophagic cargo[17,234,235]. Moreover, upon sensing cytosolic DNA, cGAS itself can interact with key regulators of autophagy, such as Beclin-1. This interaction induces autophagy through a mechanism that is independent of STING[236]. The binding of cGAS to Beclin-1 leads to the release of Rubicon, a negative regulator of autophagy, from the Beclin-1 complex. This release then facilitates the induction of autophagy, which is crucial for the removal of cytosolic DNA and the modulation of immune responses. This process is particularly important for preventing overactivation of immune responses and maintaining cellular homeostasis[236]. While the cGAS−STING pathway responds to mitochondrial stress signals, it also modulates mitochondrial function, particularly mitophagy. Activation of the cGAS−STING pathway can influence mitophagy either directly through signaling pathways affecting mitochondrial dynamics or indirectly by modulating cellular inflammatory and immune responses, which can impact mitochondrial function (Fig. 5)[237,238].

Therefore, the regulation of autophagy/mitophagy by the cGAS−STING pathway represents a critical intersection between innate immunity and cellular stress responses. This regulation ensures that cells can effectively respond to infections and damage while maintaining internal balance and preventing excessive or prolonged immune activation. Understanding these mechanisms in greater detail could provide valuable insights into developing treatments for diseases characterized by dysregulated immune responses and impaired autophagy/mitophagy, such as autoimmune disorders, neurodegenerative diseases, and certain types of cancer.

4.4. The regulatory effect of mitophagy on the cGAS−STING pathway

The regulation of the cGAS−STING pathway by autophagy/mitophagy also represents a crucial aspect of cellular homeostasis and immune response modulation. Emerging evidence suggests that autophagy/mitophagy plays significant roles in controlling the activation and function of the cGAS−STING pathway. Autophagy, which is a primary cellular defense mechanism against various stressors, including pathogens and damaged organelles, can engulf and degrade cytosolic DNA, a potent activator of the cGAS−STING pathway. By clearing cytosolic DNA, autophagy effectively regulates the activation of cGAS, preventing its overstimulation and consequent hyperactivation of immune responses[239]. This regulation is crucial for maintaining a balanced immune response, preventing chronic inflammation, and avoiding autoimmune conditions. Mitophagy, by selectively degrading damaged mitochondria, prevents the accumulation of mtDNA in the cytosol, thereby indirectly regulating the activation of the cGAS−STING pathway. The regulation of the cGAS−STING pathway by autophagy/mitophagy is complex and finely tuned (Fig. 5). It is essential for the proper functioning of the immune system, particularly in preventing excessive or inappropriate immune responses[240]. Dysregulation of this interaction can lead to various pathological conditions, including autoimmune diseases, chronic inflammatory states, and susceptibility to infections[19,240,241]. In the context of neurodegenerative diseases, such as PD and AD, the impairment of mitophagy due to mutations in genes such as Parkin and PINK1 exacerbates inflammation, contributing to the pathogenesis and progression of these disorders. Such inflammation can lead to further mitochondrial damage, creating a vicious cycle that accelerates neuronal loss[19,242]. However, research has shown that enhancing mitophagy through various means, including through NAD^+ supplementation, can counteract these effects. By reducing neuroinflammation and cellular senescence *via* the cGAS−STING pathway, these interventions offer potential therapeutic strategies that could slow or even reverse the progression of neurodegenerative diseases[242]. In addition to neurodegeneration, mitophagy and the cGAS−STING pathway are important for nonneurological diseases, where mitochondrial dysfunction and immune dysregulation play significant roles. For instance, in cardiac diseases, mitophagy deficiency leads to increased STING-mediated inflammation and pathological remodeling, highlighting the potential of targeting this pathway for therapeutic intervention[243,244]. Similarly, during aging, a decrease in mitophagy contributes to increased inflammation and cellular decline, suggesting that strategies to enhance mitophagy could help mitigate age-related diseases and prolong health[245]. Moreover, the role of mitophagy in disease is not limited to human health. Studies in model organisms, such as *Drosophila*, have provided valuable insights into the mechanisms by which mitophagy regulates immune responses and maintains cellular integrity in the face of mitochondrial damage[181]. These findings deepen our understanding of the basic biology of mitophagy and underscore the potential for cross-species therapeutic insights. Crosstalk between autophagy/mitophagy and the cGAS−STING pathway is evident in the context of pathogen clearance. Autophagy can target intracellular pathogens for degradation *via* a process known as xenophagy[241]. The cGAS−STING pathway, activated by pathogen-derived DNA, leads to an immune response. By degrading these pathogens, autophagy not only eliminates the source of infection but also the DNA that would otherwise activate the cGAS−STING pathway. This mechanism highlights the role of autophagy in modulating immune responses and maintaining cellular homeostasis. Furthermore, components of the autophagy/mitophagy machinery have been shown to interact directly with elements of the cGAS−STING pathway. For instance, the autophagy protein Beclin-1 can interact with STING, influencing its activity. This interaction suggests a more direct regulatory role of autophagy in the cGAS−STING pathway beyond just the degradation of cytosolic DNA or pathogens[236]. In summary, the regulation of innate immune responses by autophagy and mitophagy, particularly through their impact on the cGAS−STING pathway, offers a unifying theme in the pathogenesis and potential treatment of a wide array of diseases. From neurodegenerative disorders to cardiovascular diseases and the challenges of aging, this regulation ensures that immune responses are appropriately calibrated in response to cellular stress, damage, and pathogen invasion, maintaining cellular and organismal homeostasis. Further research in this area holds the potential for significant advances in our understanding of immune regulation and the development of new treatments for diseases associated with immune system dysfunction.

5. Implication of mitophagy and cGAS−STING crosstalk for neuroinflammation

The intricate interplay between cellular processes such as mitophagy and immune pathways such as the cGAS−STING axis plays a pivotal role in maintaining cellular homeostasis[242]. Within the specialized

environment of the CNS, this crosstalk has profound implications, influencing both neuroinflammatory responses and the progression of neurodegenerative diseases[232]. This section delves into the molecular interplay between mitophagy and the cGAS−STING pathway and its implications for neuroinflammation. The molecular interplay between mitophagy and the cGAS−STING pathway is central to the regulation of neuroinflammatory responses in the CNS. Disruptions in this balance, whether due to genetic predispositions, environmental factors, or age-related changes, can have profound implications for neuronal health and the progression of neurodegenerative diseases[246]. As research continues to unravel the intricacies of this crosstalk, it holds promise for the development of novel therapeutic strategies for a range of neurological conditions[242].

5.1. How the interplay between mitophagy and cGAS−STING contributes to neuroinflammation

The intricate relationship between mitophagy and the cGAS−STING pathway serves as a linchpin in the regulation of neuroinflammatory responses[232]. This interplay, rooted in the cell's need for both mitochondrial quality control and innate immune defense, has profound implications for neuronal health and function[246]. Mitochondria are dynamic organelles that are constantly undergoing fission (division) and fusion (joining). These processes are crucial for maintaining mitochondrial health, as they allow for the dilution of damaged components and the generation of new mitochondria[247]. Dysfunctional mitophagy disrupts these dynamics, leading to the accumulation of damaged and fragmented mitochondria[242]. mtDNA, due to its bacterial origin, possesses unmethylated CpG motifs, which are recognized as danger signals by the cell's innate immune system. When released into the cytoplasm, mtDNA can bind to and activate various DNA-sensing pathways, with the cGAS−STING axis being particularly sensitive[232]. By swiftly encapsulating and degrading damaged mitochondria, mitophagy acts as a gatekeeper, preventing the release of mtDNA and other mitochondrial components into the cytoplasm[246]. However, when this process is compromised, the risk of cytosolic mtDNA accumulation and subsequent immune activation increases[247].

Microglia, the primary immune cells of the CNS, are equipped with numerous sensors, including cGAS[248]. Upon sensing cytosolic mtDNA, microglia activate the cGAS−STING pathway, leading to the production of cGAMP and subsequent STING activation[242]. Activation of the cGAS−STING pathway culminates in the transcriptional upregulation of pro-inflammatory genes, leading to the release of cytokines such as IFN-β, TNF-α, and IL-6[232]. These cytokines can activate neighboring glial cells and affect neuronal function, setting the stage for chronic neuroinflammation[246]. Chronic neuroinflammation can disrupt synaptic communication, impair neurotransmitter release, and induce oxidative stress in neurons[247]. Over time, this can lead to synaptic loss, neuronal dysfunction, and even cell death[242].

In addition to its role in immune activation, STING was recently suggested to directly influence mitochondrial function[232]. Activated STING has been shown to associate with DRP1, a protein involved in mitochondrial fission that potentially influences mitochondrial dynamics[246]. The cGAS−STING pathway can modulate general autophagy[247]. For instance, sustained STING activation can inhibit autophagic flux, potentially compromising mitophagy and leading to the accumulation of damaged mitochondria[242]. The bidirectional relationship between mitophagy and the cGAS−STING pathway ensures a homeostatic balance between mitochondrial quality control and immune defense[232]. However, chronic disruptions in this balance, as observed in certain neurodegenerative diseases, can tilt the scales toward persistent neuroinflammation, exacerbating disease pathology[246].

Crosstalk between mitophagy and the cGAS−STING pathway is a testament to intricate regulatory networks in cells that ensure both energy homeostasis and defense against threats. In the specialized environment of the CNS, where energy demands are high and immune responses need to be finely tuned, understanding this interplay is crucial. Disruptions in this balance can have cascading effects on neuronal health, highlighting the importance of this molecular dialog in the context of neuroinflammation and neurodegenerative diseases (Fig. 6).

5.2. Evidence from experimental models and human studies

The interplay between mitophagy and the cGAS−STING pathway and its implications for neuroinflammation are not just theoretical constructs. Growing evidence from animal models, cellular studies, and human clinical and genetic investigations underscores the importance of this molecular crosstalk in neurodegenerative diseases[147,249]. In mouse models of AD, such as APP/PS1 mice, researchers have noted a decrease in mitophagy-related proteins such as PINK1 and Parkin, as well as an increase in cytosolic mtDNA and activation of the cGAS−STING pathway[237]. Interventions that promote mitophagy, such as overexpression of PINK1 or treatment with mitophagy-inducing compounds, reduce Aβ plaques, tau hyperphosphorylation, and neuroinflammation[71], highlighting the therapeutic potential of targeting mitophagy in AD. In models of PD, such as the MPTP-induced mouse model, there is a clear link between mitochondrial dysfunction, impaired mitophagy, and neuroinflammation[250,251]. Genetic or pharmacological enhancement of mitophagy in these models often results in reduced dopaminergic neuron loss, decreased alpha-synuclein aggregation, and attenuated neuroinflammation[93,252]. Similar observations have been made in rodent models of diseases such as HD and ALS[155,253−255]. The commonality across these models is the relationship between mitochondrial health, the cGAS−STING pathway, and neuroinflammation. In primary neuronal cultures and cell lines such as SH-SY5Y, inducing mitochondrial damage with agents such as rotenone or antimycin A leads to the release of mtDNA into the cytoplasm. This effect is often accompanied by activation of the cGAS−STING pathway, as evidenced by increased levels of cGAMP and phosphorylated TBK1[256,257]. Enhancing mitophagy, either genetically or pharmacologically, can mitigate this activation, emphasizing the protective role of mitophagy[13,19,182,255]. In glial cell cultures, especially microglia, mtDNA release following mitochondrial damage can lead to a pronounced inflammatory response accompanied by increased secretion of cytokines such as TNF-α and IL-6[69,258]. Enhancing mitophagy in these cells can dampen this inflammatory response, suggesting a potential therapeutic strategy for targeting glial-driven neuroinflammation[259,260]. Examination of brain tissues from individuals with AD, PD, or other neurodegenerative diseases often reveals evidence of mitochondrial dysfunction, with swollen and fragmented mitochondria[186,261]. Concurrently, the expression of cGAS−STING pathway components and markers of neuroinflammation are upregulated[110,172]. These findings provide direct links between human disease-related factors

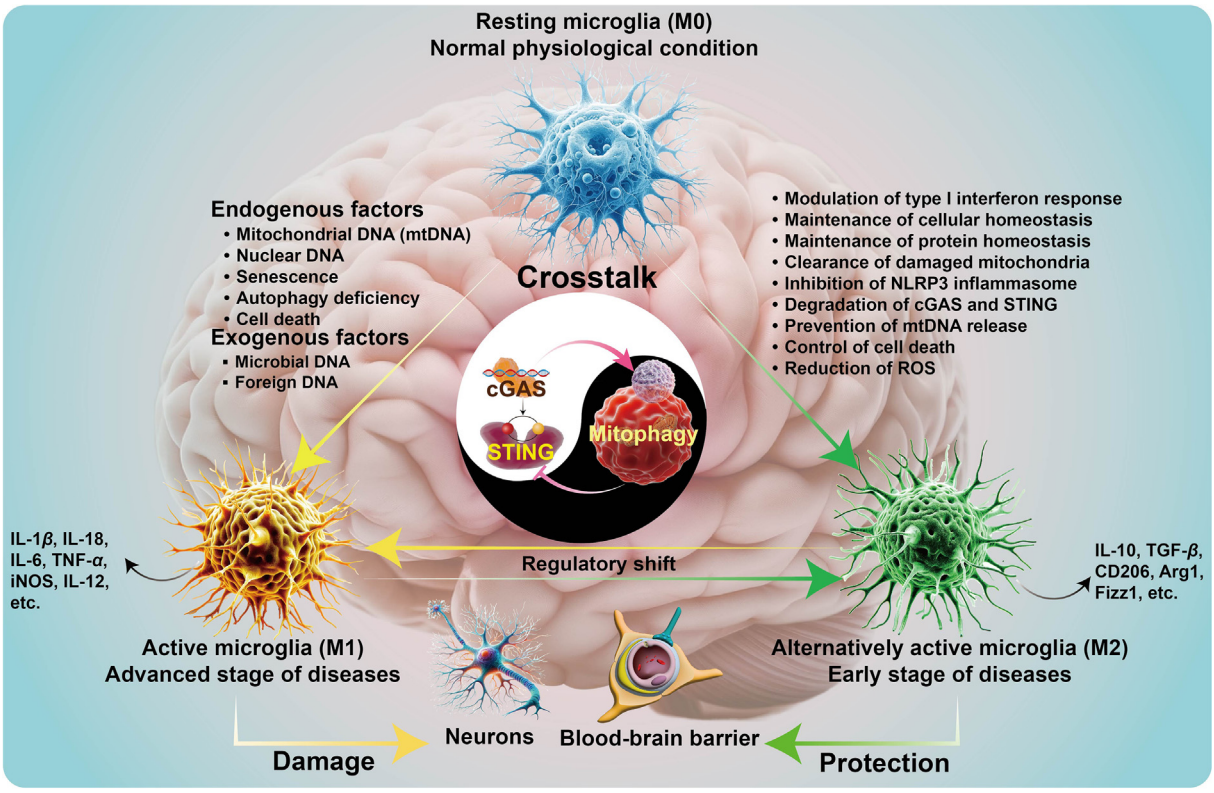

Figure 6 The role of autophagy/mitophagy and cGAS−STING crosstalk in microglial activation. In the advanced stages of neurodegenerative disease, resting M0 microglia can be activated to the M1 phenotypes under various stimuli. These include endogenous factors such as mtDNA, nuclear DNA, senescence, autophagy deficiency, and cell death, as well as exogenous factors such as microbial and foreign DNA. These factors are crucial for activating the cGAS−STING signaling pathway. In the early stages of neurodegenerative disease, resting M0 microglia can be polarized toward the M2 phenotype. This activation is achieved through the modulation of the type I IFN response, maintenance of cellular and protein homeostasis, clearance of damaged mitochondria, inhibition of the NLRP3 inflammasome, degradation of cGAS and STING, prevention of mtDNA release, control of cell death, and reduction of ROS. These processes are attributed to the induction of autophagy/mitophagy. When activated, M1 microglia release pro-inflammatory cytokines (such as TNF-α and IL-1β) and reactive species (including ROS and NO). These substances can induce neuronal damage and disrupt the integrity of the BBB. Conversely, M2 microglia release anti-inflammatory cytokines and growth factors that support neuronal survival and regeneration, and aid in the restoration and maintenance of BBB integrity.

and mitochondrial health, the cGAS−STING pathway, and neuroinflammation. Genome-wide association studies (GWASs) and targeted genetic investigations have identified mutations or variants in genes related to mitophagy, such as PINK1, Parkin, and LRRK2, in patients with neurodegenerative diseases[262−265]. Some of these genetic alterations have been linked to heightened susceptibility to diseases such as PD. Furthermore, polymorphisms in genes related to the cGAS−STING pathway have been associated with altered risk profiles for certain neurodegenerative conditions[17,266], suggesting genetic interplay between mitophagy, the cGAS−STING pathway, and disease susceptibility.

In conclusion, the evidence from experimental models and human studies paves the way for a clear picture of the intertwined relationship between mitophagy, the cGAS−STING pathway, and neuroinflammation. These findings not only enhance our understanding of the molecular underpinnings of neurodegenerative diseases but also offer promising avenues for therapeutic interventions. Targeting the crosstalk between mitophagy and the cGAS−STING pathway could pave the way for novel treatments that modulate neuroinflammation and alter the course of neurodegenerative diseases.

5.3. Potential consequences for neurodegenerative disease progression

The intricate interaction between mitophagy and the cGAS−STING pathway and its subsequent influence on neuroinflammation, has profound implications for the progression of neurodegenerative diseases. The consequences of this molecular interplay extend beyond cellular health, shaping the trajectory of disease pathology and neuronal vulnerability, and offering potential therapeutic avenues. Chronic neuroinflammation, resulting from the intertwined dysfunction of mitophagy and cGAS−STING activation, can amplify the pathological signatures of various neurodegenerative diseases. In AD, for instance, heightened neuroinflammation can enhance the enzymatic processes that lead to increased Aβ deposition[267,268]. In diseases such as PD, inflammation can promote the aggregation of alpha-synuclein, leading to the formation of Lewy bodies[269,270]. Microglia and astrocytes, the primary immune and support cells in the CNS, respectively, can become chronically activated in the face of persistent neuroinflammation[248]. This chronic activation can lead to a state in which these cells perpetually release pro-inflammatory cytokines, further

exacerbating disease pathology. Chronic activation of the cGAS−STING pathway and subsequent neuroinflammation can compromise the integrity of the BBB[271,272]. A weakened BBB can allow the entry of peripheral immune cells, toxins, and other inflammatory mediators into the CNS, further amplifying the disease's pathological processes. Chronic neuroinflammation, driven by the dysfunctional interplay between mitophagy and the cGAS−STING pathway, can increase oxidative stress within neurons. This oxidative environment can damage neuronal DNA, proteins, and lipids, impairing neuronal function and increasing the risk of cell death[273,274]. Synapses, which are crucial for neuronal communication, can become dysfunctional in an inflammatory milieu. Pro-inflammatory cytokines can disrupt synaptic plasticity, impair neurotransmitter release, and even lead to synaptic loss[275,276]. Over time, this synaptic dysfunction can manifest as cognitive deficits, memory loss, and other neurological impairments[277,278]. Certain neuronal populations, such as dopaminergic neurons in the substantia nigra in PD patients or pyramidal neurons in AD patients, are particularly vulnerable to the effects of chronic neuroinflammation. The reasons for this selective vulnerability are multifaceted and include genetic, environmental, and cellular factors[279−281]. Enhancing mitophagy through genetic means or pharmacological agents is a promising strategy for reducing the release of mtDNA and subsequent cGAS−STING activation[182,189,282]. By improving mitochondrial quality control, one can potentially attenuate neuroinflammation and slow disease progression[283]. Direct modulation of the cGAS−STING pathway *via* the use of inhibitors or activators provides another therapeutic avenue[163]. By fine-tuning the activity of this pathway, one can potentially reduce the inflammatory response and protect neuronal health. Given the multifaceted nature of neurodegenerative diseases, combination therapies targeting both mitophagy and the cGAS−STING pathway, in addition to other disease-modifying strategies, might offer the best chance for therapeutic success. The molecular crosstalk between mitophagy and the cGAS−STING pathway has significant implications for the progression of neurodegenerative disease. By dissecting these processes and their interplay, researchers and clinicians can pave the way for innovative treatments, offering new hope for individuals experiencing these challenging conditions.

6. Therapeutic potential and challenges

The intricate relationship between mitophagy and the cGAS−STING pathway, and its implications for neuroinflammation offer promising avenues for therapeutic interventions in neurodegenerative diseases. However, translating this molecular understanding into effective treatments presents both opportunities and challenges. This section delves into the current therapeutic strategies, the challenges faced in drug development and delivery, and the potential future directions in this exciting field. The molecular crosstalk between mitophagy and the cGAS−STING pathway offers rich insight into therapeutic targets for neurodegenerative diseases (Fig. 7). While significant challenges remain in translating these molecular insights into effective treatments, the potential benefits, in terms of halting or even reversing disease progression, are immense. With continued research and innovation, the coming years might witness breakthroughs that transform the therapeutic landscape for neurodegenerative diseases.

6.1. Current therapeutic strategies targeting mitophagy and the cGAS−STING pathway

The intricate interplay between mitophagy and the cGAS−STING pathway has garnered significant attention in the field of neurodegenerative disease research[13,182]. As our understanding of these processes has improved, numerous therapeutic strategies have emerged that aim to modulate these pathways for therapeutic benefit. Among these, many mitophagy activators are being explored for their potential in treating neurodegenerative diseases[92] (Table 3 and Fig. 8). UA, a metabolite produced by gut bacteria from ellagitannins and ellagic acid, has garnered increased amounts of attention for its potential therapeutic effects on neurodegenerative diseases, particularly AD and PD. In AD models, UA has been shown to reverse mitochondrial dysfunction, synaptic toxicity, and cognitive deficits induced by mutant amyloid precursor protein (APP) and Aβ, as well as by phosphorylated tau (p-tau). Notably, UA stimulated mitophagy and promoted the elimination of defective mitochondria in the hippocampus of AD mice, improving mitochondrial morphology and size. This enhancement of mitophagy was associated with significant improvements in learning and memory retention, as evidenced by the Morris water maze test and the Y maze spontaneous alternation behavioral test. UA treatment also led to a reduction in common AD pathological features, including insoluble levels of Aβ_{1-42} and Aβ_{1-40} and an increase in the extracellular Aβ plaque burden. Furthermore, UA inhibited inflammation in microglia isolated from APP/PS1 mice *via* PINK-1-dependent mitophagy, indicating its role in reducing neuroinflammation associated with AD[71,209,284,285]. In an MPTP-induced mouse model of PD, UA reduced dopaminergic neuron loss, ameliorated behavioral deficits, and attenuated neuroinflammation. Additionally, UA promoted mitophagy and suppressed NLRP3 inflammasome activation in microglia, restoring mitochondrial function and inhibiting pro-inflammatory responses[89]. Melatonin (MT), a hormone primarily known for regulating the sleep-wake cycle, has emerged as a promising therapeutic agent for AD due to its potential to enhance mitophagy and regulate inflammation. Research indicates that MT can improve cognitive deficits and mitochondrial dysfunction in AD models by promoting the removal of damaged mitochondria and reducing Aβ pathology, thereby improving mitochondrial function and cognition[28]. Additionally, MT regulates NLRP3 inflammasome activity, which is linked to AD progression, by inducing the nuclear translocation of transcription factor EB (TFEB), which plays a crucial role in autophagy and mitophagy. This action leads to decreased ROS, reduced senile plaque formation, and decreased inflammatory cytokine levels, highlighting the potential of MT for mitigating AD symptoms and progression[286]. Rapamycin (Rapa), a well-known autophagy and mitophagy enhancer, has demonstrated significant neuroprotective effects on various models of neurodegenerative diseases and injuries, including AD, I/R, and spinal cord ischemia−reperfusion injury (SCIRI). In AD models, Rapa was shown to activate Parkin-mediated mitophagy, enhancing the clearance of damaged mitochondria and improving cognitive and synaptic plasticity deficits in APP/PS1 mice. This action leads to improved learning and memory and synaptic function and reduced oxidative stress and apoptosis, suggesting a pivotal role for mitophagy in alleviating AD pathology[287]. Similarly, in models of cerebral ischemia, Rapa enhanced mitophagy, as evidenced by

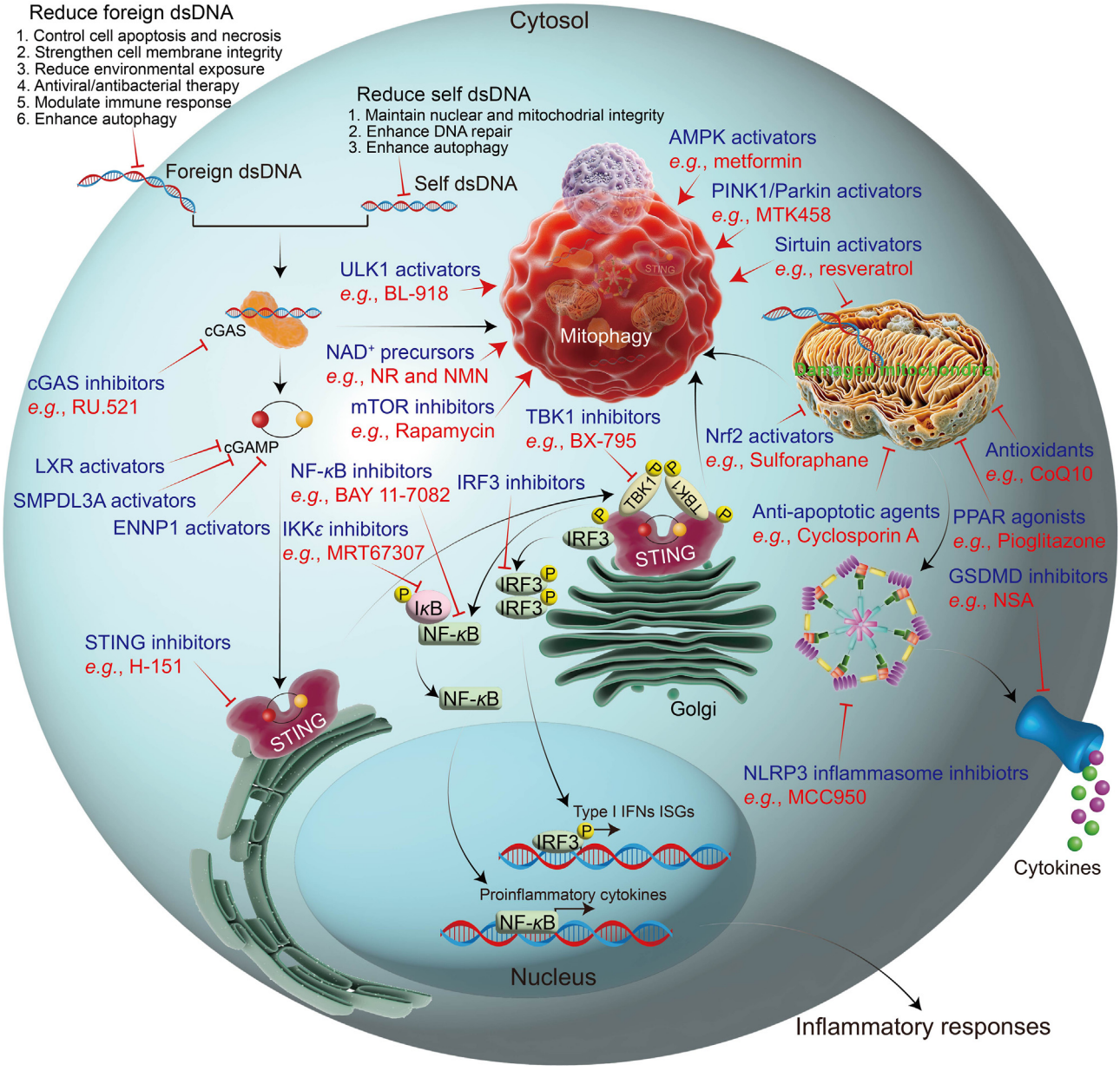

Figure 7 Potential therapeutic targets and interventions focusing on the crosstalk between autophagy/mitophagy and the cGAS−STING pathway could be pivotal in mitigating the inflammatory responses associated with neurodegenerative diseases. By detecting dsDNA and subsequently activating the cGAS−STING pathway, this overview provides potential intervention sites. These include reducing foreign and self-dsDNA, targeting compounds that inhibit the cGAS−STING−TBK1 signaling pathway, targeting compounds that activate autophagy/mitophagy, targeting compounds that protect mitochondria, and targeting compounds that inhibit NLRP3 inflammasome-mediated pyroptosis.

increased LC3-II and Beclin-1 expression, reduced mitochondrial dysfunction and infarct volume, and improved neurological outcomes, linking enhanced mitophagy to mitochondrial protection and neuroprotection[288]. Furthermore, in the context of SCIRI, Rapa significantly increased mitophagy, as indicated by the translocation of p62 and Parkin to damaged mitochondria and attenuated mitochondria-dependent apoptosis. This resulted in reduced apoptosis and improved locomotor function, highlighting the therapeutic potential of Rapa in spinal cord injury through the promotion of mitophagy and inhibition of apoptosis[289]. Resveratrol (RVT), a naturally occurring polyphenol found in grapes and other plants, has garnered attention for its potential neuroprotective effects on various models of neurodegenerative diseases, including AD and cerebral ischemia. The underlying mechanisms through which RVT exerts its protective effects have been the subject of extensive research, with a particular focus on its ability to enhance mitophagy. In the context of AD, RVT was shown to attenuate oxidative damage, enhance mitophagy, and reduce apoptosis in $A\beta_{1-42}$-treated PC-12 cells, suggesting that the activation of mitophagy plays a crucial role in the neuroprotective mechanism of RVT[290]. Similarly, in a model of oxygen/glucose deprivation/reoxygenation (OGD/R), a simulation of cerebral ischemia, RVT improved cell viability, suppressed apoptosis, and alleviated oxidative stress and mitochondrial damage through the induction of mitophagy. This was further supported by the activation of the PINK1/Parkin pathway,

Table 3 Pharmacological activity and mechanism of action of mitophagy activators in neurodegenerative diseases.

Inhibitor	Cell and animal	Pharmacological activity	Disease
MT	5xFAD mice	Ameliorates cognitive impairments and mitochondrial dysfunction and decreases Aβ deposition in the brain of 5 × FAD mice; attenuates mitophagy deficits by promoting the fusion of mitophagosomes and lysosomes in the hippocampus of 5 × FAD mice	AD[28]
MT	APP/PS1 mice; $A\beta_{25-35}^{-}$ induced SH-SY5Y cells	Improves the cognitive function of APP/PS1 mice; decreases ROS and senile plaque in APP/PS1 mice; inhibits the activation of the NLRP3 inflammasome; promotes mitophagy in APP/PS1 mice and SH-SY5Y cells by inducing TFEB nuclear translocation	AD[286]
RVT	$A\beta_{42}$-induced PC-12 cells	Inhibits cell apoptosis, oxidative damage, and mitochondrial damage; promotes mitophagy by increasing Parkin and Beclin-1 expression	AD[290]
RVT	OGD/R-induced rat cortical neurons	Improves cell viability and suppresses apoptosis; alleviates mitochondrial membrane potential and excessive oxidative stress; promotes mitophagy by activating the PINK1/Parkin pathway	I/R[291]
UA	CL2355 worms; APP/PS1 mice; apolipoprotein E4 iPSC-derived neurons; mAPP-HT22 cells; mTau-HT22 cells	Improves cognitive function of worms and APP/PS1 mice; reduces Aβ peptides in worms; maintains mitochondrial healthy in mAPP-HT22 cells, mTau-HT22 cells, and the hippocampus of APP/PS1 mice; diminishes insoluble levels of $A\beta_{1-42}$ and $A\beta_{1-40}$, and extracellular Aβ plaque; increases the maximal oxygen consumption rate of apolipoprotein E4 neurons; increases the phagocytic efficiency of microglia; mitigates the NLRP3 inflammasome-dependent neuroinflammation; inhibits tau hyperphosphorylation in SH-SY5Y and enhances memory in tau worms and 3 × *Tg* AD mice; promotes mitophagy by activating the PINK1/Parkin pathway	AD[284,285]
AC	CL2355 worms; APP/PS1 mice; mAPP-HT22 cells; mTau-HT22 cells	Improves cognitive function of worms and APP/PS1 mice; maintains mitochondrial healthy in mAPP-HT22 cells, mTau-HT22 cells, and the hippocampus of APP/PS1 mice; diminishes insoluble levels of $A\beta_{1-42}$ and $A\beta_{1-40}$, and extracellular Aβ plaque; increases the phagocytic efficiency of microglia; mitigates the neuroinflammation of APP/PS1 mice; promotes mitophagy by activating the PINK1/Parkin pathway	AD[71,284,285]
NAD^{+} supplementation	CL2355 worms; APP/PS1 mice; mAPP-HT22 cells; mTau-HT22 cells	Improves associative memory of worms; maintains mitochondrial health in mAPP-HT22 cells and mTau-HT22 cells; promotes mitophagy by activating the *dct-1* and PINK1/Parkin pathway	AD[71,284,285]
Tomatidine	mAPP-HT22 cells; mTau-HT22 cells	Maintains mitochondrial health in mAPP-HT22 cells and mTau-HT22 cells; promotes mitophagy by activating the PINK1/Parkin pathway	AD[71,284,285]
EGCG, or UA + EGCG	mTau-HT22 cells	Maintains mitochondrial health in mTau-HT22 cells; promotes mitophagy by activating the PINK1/Parkin pathway	AD[284]
Rapa	APP/PS1 mice	Improves cognitive function; synaptic plasticity, and the expression of synapse-related proteins; inhibits cytochrome C-mediated apoptosis and oxidative damage; recovers mitochondrial function; promotes mitophagy by increasing p62 and Parkin protein expressions	AD[287]
KPF and rhapontigenin	CL2355 and BR5270 worms; HEK 293 3G-EGFP-Tau P301L/mCherry; 3x*Tg* AD mice	Increases the survival and functionality of glutamatergic and cholinergic neurons; inhibits Aβ and tau pathologies; improves the cognitive function of 3 × *Tg* AD mice; promotes mitophagy by activating the PINK1/Parkin pathway	AD[295]

(*continued on next page*)

Table 3 (*continued*)

Inhibitor	Cell and animal	Pharmacological activity	Disease
UMI-77	APP/PS1 mice	Ameliorates cognitive decline and amyloid pathologies; reduces neuroinflammation; promotes mitophagy by promoting the activation of MCL-1 with LC3A and *Atg5*	AD[76]
Bexarotene	Human induced pluripotent stem cells derived NSCs	Eliminates dysfunctional mitochondria and restores the mitochondrial network morphology; promotes mitophagy by activating the PINK1/Parkin pathway	AD[302]
β-Asarone	Aβ_{42}-treated rats	Improves the learning and memory of rats; promotes mitophagy by activating the PINK1/Parkin pathway	AD[303]
Deoxytrillenoside CA and epitrillenoside CA	EGFP-N1-APP, EGFP-Tau-WT-, or EGFP-Tau-P301L-transfected HT-22 cells; CL2331, CL4176, BR5270, NL5901, 6-OHDA-induced BZ555; and AM141 worms; APP/PS1 mice	Improve the cognitive function and behaviors in worms and mouse models of AD, PD, and HD; inhibit Aβ and tau pathologies *in vivo* and *in vitro* of AD models; inhibit α-synuclein and mHtt in worm models of PD and HD; inhibits the loss of dopaminergic neurons in 6-OHDA-induced BZ555 worms; promote mitophagy by activating the AMPK/ULK1, mTOR, and PINK1/Parkin pathways	AD, PD, HD[293,294]
Spermidine	NL5901 worms; UM0001 worms	Ameliorates behavioral deficits and pathological features in NL5901 worms; prolongs lifespan and protects against memory loss in UM0001 worms; promotes mitophagy by activating the PINK1/Parkin pathway	AD, PD[304]
UA	LPS-BV2; MPTP-induced mice	Reduces the loss of dopaminergic neurons; ameliorates behavioral deficits and neuroinflammation in MPTP-induced mice; restores mitochondrial function and attenuates pro-inflammatory response in LPS-induced BV-2 cells; inhibits the NLRP3 inflammasome *in vivo* and *in vitro*	PD[89]
QU	LPS/ATP-induced BV2 and primary microglia; LPS-treated mice	Inhibits the NLRP3 inflammasome-mediated neuroinflammation *in vitro* and *in vivo* models; inhibits the NF-κB signaling pathway; eliminates damaged mitochondria and reduces mitochondrial ROS levels; promotes mitophagy by activating the PINK1/Parkin pathway	PD[91]
QU	6-OHDA-treated rats; 6-OHDA-induced PC12 cells; NL5901 and 6-OHDA-induced BZ555 worms	Alleviates PD-like motor behaviors, mitigates neuronal death, and reduces mitochondrial damage and α-synuclein accumulation in 6-OHDA-treated rats; improves mitochondrial quality control, reduces oxidative stress, and decreases α-synuclein expression in 6-OHDA-treated PC12 cells; promotes mitophagy by activating the PINK1/Parkin pathway	PD[292]
Justicidin A, justicidin B, and justicidin C	6-OHDA-induced PC-12 or SHSY5Y cells; α-synuclein overexpressing MEF cells; 6-OHDA-induced rats	Inhibit 6-OHDA-induced cell death, mitochondrial damage, and oxidative damage; degrade α-synuclein expression *via Atg7*; inhibit α-synuclein expression and reduce the loss of dopaminergic neurons; improve behaviors in worm and rat models of PD; Promote mitophagy by activating the AMPK/ULK1, Raf/MEK/ERK, and PINK1/Parkin pathways	PD[93]
Rapa	MCAO rats	Reduces infarct volume, improves neurological outcomes, and inhibits mitochondrial dysfunction in MCAO rats; promotes mitophagy by increasing p62 protein expression	I/R[288]
Rapa	SCIRI mice	Improves the locomotor function; decreases mitochondrial apoptosis and reduces the TUNEL + cells in the spinal cord ischemic tissue; promotes mitophagy by increasing p62 and Parkin protein expressions	I/R[289]

6-OHDA, 6-hydroxydopamine; Aβ, amyloid beta; AC, actinonin; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; *Atg5*, autophagy-related gene 5; *Atg7*, autophagy-related gene 7; HD, Huntington's disease; I/R, ischemia/reperfusion; KPF, kaempferol; LPS, lipopolysaccharide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; MT, melatonin; NF-κB nuclear factor-kappa B; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; OGD/R, oxygen/glucose deprivation/reoxygenation; PD, Parkinson's disease; QU, quercetin; Rapa, rapamycin; ROS, reactive oxygen species; RVT, resveratrol; SCIRI, spinal cord ischemia−reperfusion injury; TFEB, transcription factor EB; MCAO, middle cerebral artery occlusion; UA, urolithin A.

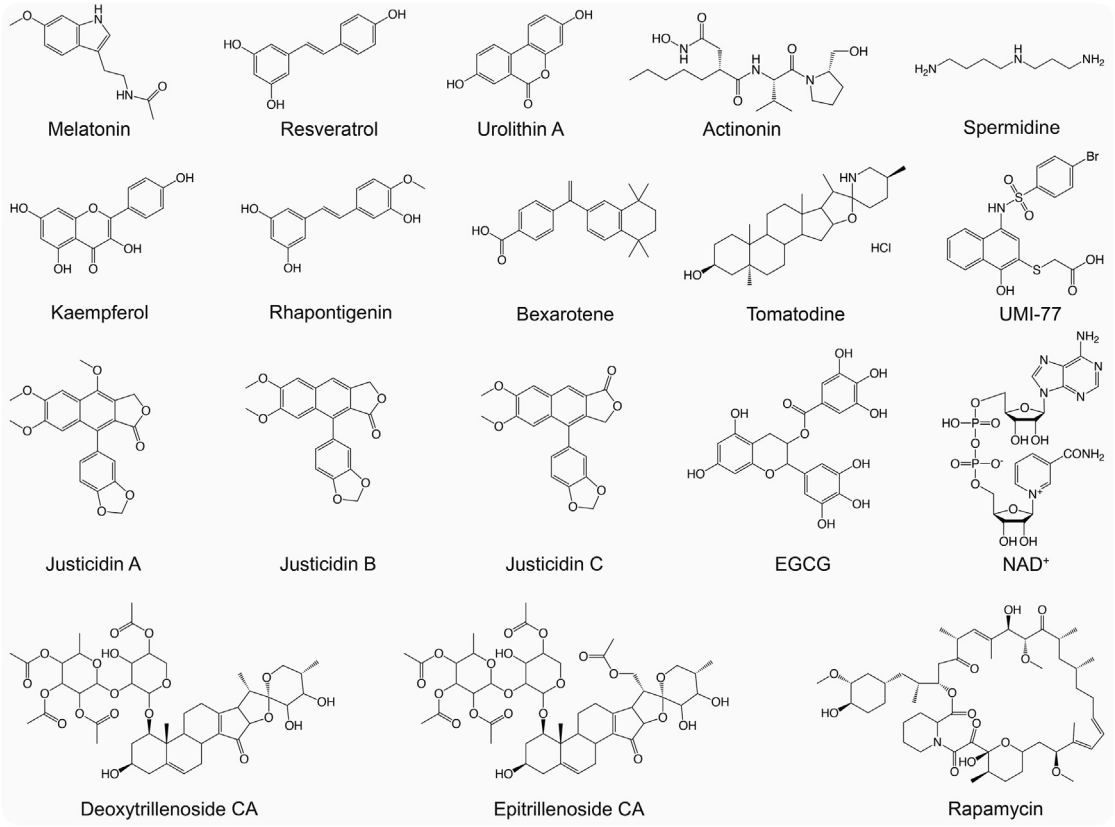

Figure 8 The chemical structures of mitophagy activators are used in various neurological diseases.

indicating that the protective effects of RVT against OGD/R-related damage are mediated, at least in part, by promoting mitophagy[291]. Moreover, other natural compounds, such as quercetin (QU), justicidin A, justicidin B, justicidin C, deoxytrillenoside CA, epitrillenoside CA, kaempferol (KPF), and rhapontigenin, have also been shown to activate mitophagy and exhibit neuroprotective effects in various neurodegenerative diseases[91,93,292–295]. On the other hand, inhibitors targeting the cGAS−STING pathway have potential applications in treating autoimmune diseases such as neurovegetative diseases by modulating the immune response and inflammation (Table 4). The chemical structures of the currently reported inhibitors of cGAS, STING, and TBK1 and inhibitors of the nuclear factor-κB (IκB) kinase are displayed in Fig. 9. For example, as a direct inhibitor of cGAS, RU.521 prevents the synthesis of cGAMP, thereby dampening the downstream activation of STING and the associated inflammatory cascade[296]. Its potential in treating neurodegenerative diseases lies in its ability to reduce chronic neuroinflammation, which exacerbates neuronal damage[272]. By targeting STING directly, H-151 can inhibit the downstream effects of cGAS activation[297]. By doing so, it can mitigate the production of pro-inflammatory cytokines and type I IFNs, offering neuroprotection[147,298]. In addition to direct inhibitors, strategies that modulate the downstream effectors of the cGAS−STING pathway, such as TBK1 or IRF3, can also offer therapeutic benefits[299–301]. By targeting these molecules, one can fine-tune the inflammatory response, balancing immune activation with neuroprotection. The bidirectional relationship between mitophagy and the cGAS−STING pathway offers a unique therapeutic opportunity. By simultaneously enhancing mitophagy and inhibiting the cGAS−STING pathway, one can achieve a synergistic effect, offering enhanced neuroprotection compared to modulating either pathway alone. Combining agents such as UA or NAD^+ with cGAS−STING inhibitors can potentially amplify their benefits. Such combinations can ensure that while damaged mitochondria are efficiently removed, any released mtDNA does not trigger a robust inflammatory response. Combining genetic strategies, such as overexpressing PINK1 or Parkin, with pharmacological inhibitors of the cGAS−STING pathway can offer a multipronged approach to neuroprotection. Such strategies can ensure both enhanced mitochondrial quality control and dampened neuroinflammation. In conclusion, the therapeutic landscape targeting mitophagy and the cGAS−STING pathway is vast and rapidly evolving. As our understanding of these processes deepens and as new modulators are identified, the potential to halt or even reverse the progression of neurodegenerative diseases becomes increasingly tangible. In the coming years, exciting advancements in this realm will be made, offering hope to millions affected by these debilitating conditions.

6.2. *Challenges in drug development and delivery*

The quest to develop effective treatments for neurodegenerative diseases, especially those involving targeting processes such as mitophagy and the cGAS−STING pathway, is fraught with challenges. These challenges span from the fundamental barriers

Table 4 Pharmacological activity and mechanism of action of inhibitors targeting cGAS−STING−TBK1 signaling in neurodegenerative diseases.

Inhibitor	Cell and animal	Pharmacological activity and mechanism of action	Disease
H-151	Primary microglia, neurons, and astrocytes; 5xFAD mice	Inhibits oligomeric Aβ_{42}-induced neuronal toxicity; lowers Aβ_{42}, and Aβ cores in DG and cortex, and reduces *Iba1*$^{+}$ microglia and GFAP $^{+}$ astrocytes in DG, boosting microglial phagocytosis	AD[147]
RU.521	Primary neurons	Inhibits oligomeric Aβ_{42}-induced neuronal toxicity	AD[147]
H-151	Primary microglia and BV2; Aged and mg-*Cgas*^{R241E} mice	Reduces hippocampal *Iba1*$^{+}$ cells; Boosts hippocampal *NeuN*$^{+}$ cells and synaptophysin in CA1; suppresses IFN signaling and microglial function genes in aged mice; inhibits I/R-induced cGAS-dependent inflammation; lessens learning decline in mg-*Cgas*^{R241E} mice	Aging[163]
RU.521	TDP-43-overexpressing THP-1 cells	Reduces IFN-β and TNF-α expression in mutant TDP-43 overexpressing THP-1 cells	ALS[155]
H-151	TDP-43-overexpressing THP-1 cells, iPSC-derived motor neurons, TDP-43 mutant mice	Reduces IFN-β and TNF-α in mutant TDP-43 THP-1 cells; reduces motor neuron death in iPSC-derived neurons; decreases IFN and NF-κB in the cortex and spinal cord, lessens neuron loss in cortical layer V, and enhances behavior in TDP-43 mutant mice	ALS[155]
H-151	PBMCs and monocyte-derived macrophage	Maintains basal ISG expression in sporadic ALS PBMCs, while effectively suppressing ISG in C9-ALS PBMCs and monocyte-derived macrophage	ALS/FTD[156]
H-151	Primary microglia, BV2, and monocytes; MCAO mice	Reduces cGAS expression, absent in melanoma 2 inflammasome, and pyroptosis-related molecules; inhibits immune response poststroke, reducing neutrophils, microglia, and IL-6 and TNF-α production; lessens infarct volume, neurologic deficits, and cell death	Stroke[159]
RU.521	Ferric chloride-induced male C57BL/6J mice	Lowers 2′,3′-cGAMP, STING, and inflammatory cytokines; inhibits NLRP3 inflammasome; reduces oxidative stress and microglia/neutrophil numbers; improves neuronal health and neurological function post-CVST	CVST[168]
RU.521	BV-2; SNI-induced rats	Diminishes cGAS, STING, p-IRF3, p-NF-κB, CD16, IL-1β, and TNF-α, and increases *Mrc1* and *Il10* mRNAs in LPS-induced BV-2 cells; increases PMTs, lowers mechanical hyperalgesia index, reduces cGAS, STING, p-IRF3, p-NF-κB, IFN-β, Iba1, CD16, IL-1β and TNF-α, and increases *Mrc1* and *Il10* in SNI rats	Neuropathic pain[169]
C-176	BV-2; SNI-induced rats	Diminishes STING, p-IRF3, p-NF-κB, CD16, IL-1β, and TNF-α, and increases *Mrc1* and *Il10* mRNAs in LPS-induced BV-2 cells; increased PMTs, increases PMTs, lowers mechanical hyperalgesia index, reduces STING, p-IRF3, p−NF-κB, IFN-β, Iba1, CD16, IL-1β and TNF-α, and increases CD206 and IL-10 in SNI rats	Neuropathic pain[169]
H-151	Mixed microglia and astrocyte cultures	Inhibits the expression of pTBK1	PD[152]
RU.521	MPTP-induced WT and *Cgas*$^{-/-}$ mice	Eases PD symptoms; lessens tyrosine hydroxylase-positive neuron loss; decreases activated microglia in the SN; reduces cGAS-dependent inflammation factors	PD[153]
RU.521	C20 and SIM-49 cells; SOD1^{G93A} mice	Reduces *Ifn-β* mRNA in SOD1^{G85R} and SOD1^{G93A} transfected C20 cells and HT-DNA treated C20 cells; inhibits IFN-β reporter activities in SOD1^{G93A} SIM-49 cells; enhances weight, delays disease onset, increases survival rate, improves motor function, and reduces IFN, ISG, pro-inflammatory, and chemokine gene mRNA in SOD1^{G93A} mice brains and spinal cords	ALS[157]
H-151	C20 and SIM-49 cells; SOD1^{G93A} mice	Reduces *Ifn-β* mRNA in SOD1^{G85R} and SOD1^{G93A} transfected C20 cells and HT-DNA treated C20 cells; inhibits IFN-β and NF-κB reporter activities in SOD1^{G93A} SIM-49 cells; reduces *Ifnb1*, *Rsad2*, and *Il6* mRNA in SOD1^{G93A} mice spinal cord	ALS[157]
C-176	SIM-49 cells; SOD1^{G93A} mice	Inhibits IFN-β reporter activities in SOD1^{G93A} SIM-49 cells; enhances weight, delays disease onset, increases survival rate, improves motor function, and reduces *Ifnb1*, *Rsad2*, and *Il6* mRNA in SOD1^{G93A} mice spinal cord	ALS[157]

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CVST, cerebral venous sinus thrombosis; DG, dentate gyrus; IFN-β, interferon-beta; IL-10, interleukin 10; ISG, interferon-stimulated genes; LPS, lipopolysaccharide; NF-κB, nuclear factor-kappa B; PBMCs, peripheral blood mononuclear cells; SN, substantia nigra; SNI, spared nerve injury; SOD1, superoxide dismutase type 1; TDP-43, TAR DNA-binding protein 43; TNF-α, tumor necrosis factor-alpha.

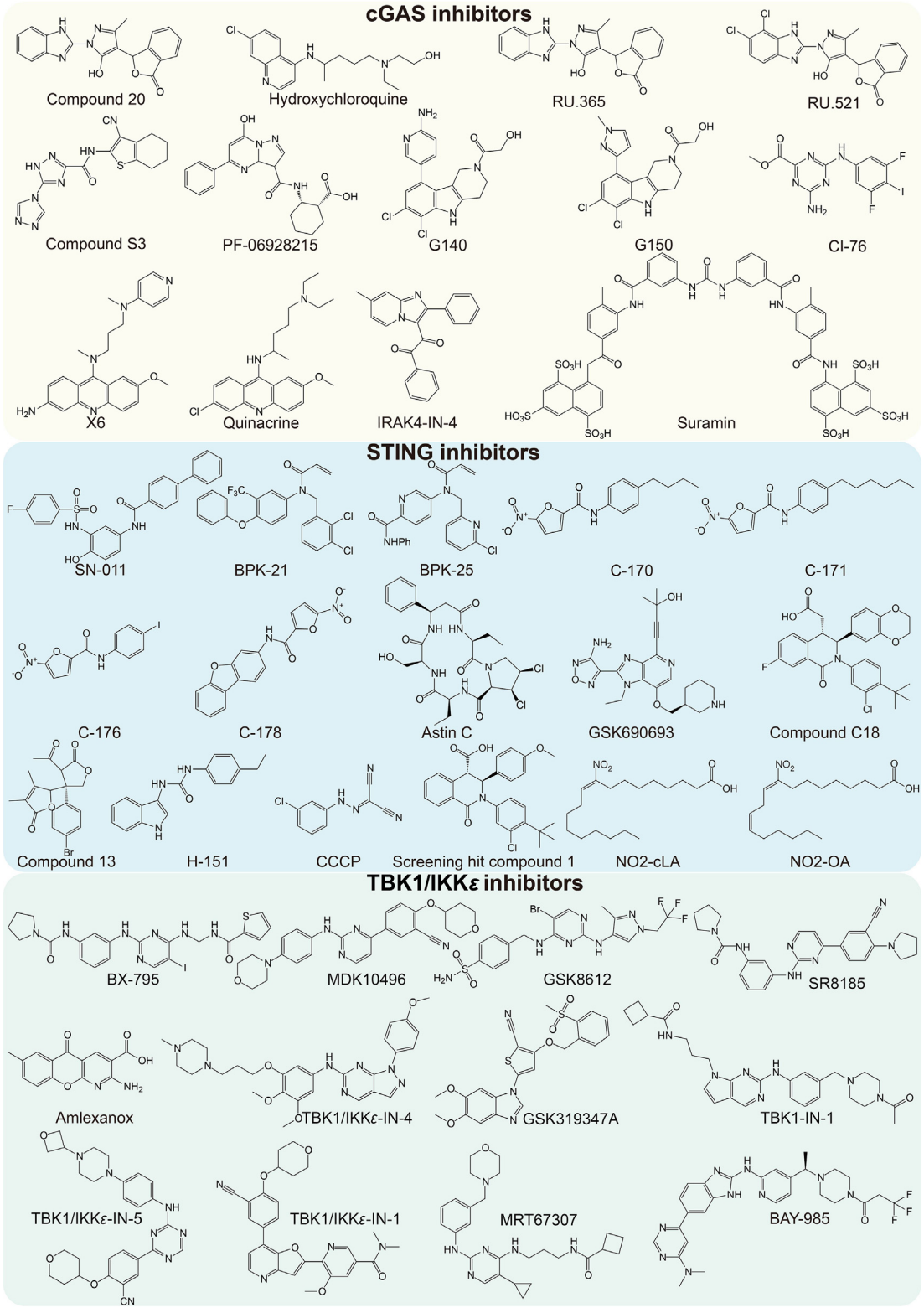

Figure 9 The chemical structures of the identified cGAS, STING, TBK1, and IκB kinase ε (IKKε) inhibitors targeting the cGAS−STING−TBK1 signaling pathway.

posed by the brain's protective mechanisms to the intricacies of individual genetic variability[305,306]. Addressing these challenges is crucial for the successful translation of promising laboratory findings into clinical therapeutics. The BBB, a tightly regulated barrier formed by endothelial cells, astrocytes, and pericytes, is designed to protect the brain from potential toxins and pathogens[306]. This barrier selectively restricts the entry of molecules based on size, charge, and lipid solubility. Despite showing

promise *in vitro*, many therapeutic agents struggle to reach therapeutic concentrations in the brain due to their inability to traverse the BBB. To overcome BBB restrictions, drug design often involves modifications to enhance lipid solubility or to enable transport *via* endogenous transporters[307,308]. However, such modifications can sometimes compromise the efficacy of the drug or introduce new side effects[309]. Strategies such as intranasal delivery[310], convection-enhanced delivery[311], or the use of nanoparticles aim to bypass the BBB[312], but each approach involves its own set of challenges and limitations. The cellular pathways involved in mitophagy and the cGAS−STING axis are intricate and involve multiple proteins and intermediates. Drugs that target one component without affecting others require drugs with high molecular specificity, which is a challenge in drug design. The cGAS−STING pathway, while implicated in neuroinflammation, also plays a role in systemic immunity[313]. Inhibiting this pathway might render individuals more susceptible to infections or other diseases, necessitating a careful balance between therapeutic benefits and potential risks[314]. Chronic modulation of fundamental cellular processes can have ripple effects throughout the cell and the organism. For instance, while enhancing mitophagy might offer neuroprotection, it could also influence other forms of autophagy or cellular processes, with unforeseen consequences[40]. Even after rigorous clinical trials, the long-term effects of a new drug might become apparent only after it has been used by a broader population for an extended period. Robust post-marketing surveillance systems are crucial for monitoring and addressing any emerging safety concerns[315]. Individuals can vary significantly in their response to drugs, a variability often rooted in genetic differences[316]. For instance, polymorphisms in drug-metabolizing enzymes can influence drug efficacy and safety profiles[317]. As our understanding of the genetic underpinnings of neurodegenerative diseases grows, there is a move toward personalized medicine[317]. This approach tailors treatments based on an individual's genetic makeup, optimizing therapeutic outcomes. However, complex drug development also exists, requiring therapies to be tested across diverse genetic backgrounds[317]. Personalized medicine, while promising, also raises ethical concerns, especially regarding data privacy and the potential for genetic discrimination[318]. In conclusion, while the challenges in drug development and delivery for neurodegenerative diseases are significant, they are not insurmountable. Advances in technology, a deeper understanding of disease mechanisms, and collaborative efforts between researchers, clinicians, and patients will pave the way for innovative solutions. As we address these challenges, the horizon holds the promise of transformative therapies that can change the trajectory of neurodegenerative diseases, offering hope to millions worldwide.

7. Perspectives and conclusions

As we delve into the intricate landscape of neuroinflammation, the critical dialog between mitophagy and the cGAS−STING pathway presents both challenges and a wealth of therapeutic opportunities. This interplay is crucial for neuronal function, where efficient mitophagy is essential for clearing damaged mitochondria, and the cGAS−STING pathway, though a defender against pathogens, can lead to sustained neuroinflammation and neurodegeneration when dysregulated.

In addressing these challenges, several promising directions have emerged:

(1) Nanotechnology and drug delivery

Advancements in nanocarriers, such as nanoparticles and liposomes, provide innovative means to encapsulate and deliver therapeutic agents across the restrictive BBB[319−321]. The potential of these materials for targeted delivery and sustained release of drugs offers strategic advantages, particularly for treatments with narrow safety margins[322]. For instance, nanotechnology-enhanced RVT delivery systems, such as biomimetic nanosystems and nanostructured hydrogels, offer a promising approach to treating neurodegenerative diseases. They ensure targeted and efficient delivery to neuronal mitochondria and the brain. These advancements significantly improve the therapeutic efficacy of RVT against AD and PD by overcoming the limitations of traditional treatments and enhancing biocompatibility and drug circulation. This innovative strategy highlights the potential of nanotechnology for revolutionizing neuroprotective therapy[323−325].

(2) Gene therapy and precision medicine

The advent of CRISPR-Cas9 and other gene-editing technologies ushers in a new era of precision medicine, capable of correcting genes implicated in dysfunctional mitophagy or aberrant cGAS−STING activation[326,327]. These modalities promise long-lasting benefits, but their delivery methods must be refined for safe and efficient CNS targeting[328]. For instance, aging mice lacking the STING protein (STING1$^{-/-}$) exhibit reduced microglial accumulation and increased neuron density in the hippocampus. Additionally, both aged STING1$^{-/-}$ mice and cGAS-knockout BV-2 microglia exhibit decreased levels of pro-inflammatory markers, including IL-1β, IL-6, and TNF-α[163].

(3) Biomarker development and personalized therapeutics

The identification of biomarkers, ranging from genetic to metabolic, can inform disease progression and therapeutic responses[329]. Personalizing treatments based on these biomarkers could substantially improve patient outcomes by optimizing efficacy and reducing adverse effects. For instance, the levels of specific cytokines or mtDNA fragments in cerebrospinal fluid could serve as indicators of cGAS−STING activation and mitophagy efficiency[330].

(4) Stem cell therapies and regenerative medicine

The potential of stem cells to differentiate and replace damaged neurons, or to support existing ones offers a beacon of hope[331,332]. When combined with interventions that modulate mitophagy and the cGAS−STING pathway, stem cell therapies enhance the efficacy and integration of drugs within the CNS. For instance, RVT significantly enhances the engraftment and therapeutic effects of human umbilical cord-derived mesenchymal stem cells in a mouse model of AD. This combination not only improved cognitive functions but also increased neuroprotection through mechanisms involving neurotrophic secretion, neurogenesis, and the activation of SIRT1 signaling pathways in the hippocampus, suggesting that RVT is a promising approach for treating AD[333].

Despite these forward-looking strategies, substantial challenges need to be addressed. A comprehensive understanding of the roles these pathways play in neuroinflammation is needed. Overcoming hurdles such as drug delivery to the CNS, specificity,

safety, and systemic immune impact is critical for translating preclinical findings into clinical applications. The future holds exciting possibilities for innovative therapies. Collaborative efforts across disciplines will be vital for the development of effective treatments. Ethical considerations will guide the progression of genetic interventions and personalized medicine.

In conclusion, crosstalk between mitophagy and the cGAS−STING pathway is a pivotal process in neuroinflammation and neurodegenerative diseases. Unveiling its intricacies and realizing its therapeutic potential demands a united effort from the global scientific community. With these concerted efforts, we are moving closer to novel treatments and improving the quality of life for individuals with neurodegenerative diseases.

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Author contributions

Xiaogang Zhou: Data curation, Writing − original draft, Writing − review & editing. Jing Wang: Investigation, Software, Writing − original draft. Lu Yu: Investigation, Visualization. Gan Qiao: Investigation, Visualization. Dalian Qin: Visualization. Betty Yuen-Kwan Law: Investigation. Fang Ren: Supervision, Writing − review & editing. Jianming Wu: Funding acquisition, Supervision, Writing − review & editing. Anguo Wu: Funding acquisition, Software, Supervision, Writing − review & editing.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Amor S, Puentes F, Baker D, van der Valk P. Inflammation in neurodegenerative diseases. *Immunology* 2010;**129**:154−69.
2. Zhou XG, Qiu WQ, Yu L, Pan R, Teng JF, Sang ZP, et al. Targeting microglial autophagic degradation of the NLRP3 inflammasome for identification of thonningianin A in Alzheimer's disease. *Inflamm Regen* 2022;**42**:25.
3. Brown GC, Neher JJ. Microglial phagocytosis of live neurons. *Nat Rev Neurosci* 2014;**15**:209−16.
4. Engelhardt B, Ransohoff RM. Capture, crawl, cross: the T cell code to breach the blood−brain barriers. *Trends Immunol* 2012;**33**:579−89.
5. He X, Wang X, Yang L, Yang Z, Yu W, Wang Y, et al. Intelligent lesion blood−brain barrier targeting nano-missiles for Alzheimer's disease treatment by anti-neuroinflammation and neuroprotection. *Acta Pharm Sin B* 2022;**12**:1987−99.
6. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015;**523**:337−41.
7. Ransohoff RM. How neuroinflammation contributes to neurodegeneration. *Science* 2016;**353**:777−83.
8. DiSabato DJ, Quan N, Godbout JP. Neuroinflammation: the devil is in the details. *J Neurochem* 2016;**139**(Suppl 2):136−53.
9. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol* 2015;**14**:388−405.
10. McGeer PL, McGeer EG. Inflammation and neurodegeneration in Parkinson's disease. *Parkinsonism Relat Disorders* 2004;**10**(Suppl 1):S3−7.
11. Liu J, Wang F. Role of neuroinflammation in amyotrophic lateral sclerosis: cellular mechanisms and therapeutic implications. *Front Immunol* 2017;**8**:1005.
12. Wang B, Ma Y, Li S, Yao H, Gu M, Liu Y, et al. GSDMD in peripheral myeloid cells regulates microglial immune training and neuroinflammation in Parkinson's disease. *Acta Pharm Sin B* 2023;**13**:2663−79.
13. Li C, Zhu Y, Liu W, Xiang W, He S, Hayashi T, et al. Impaired mitophagy causes mitochondrial DNA leakage and STING activation in ultraviolet B-irradiated human keratinocytes HaCaT. *Arch Biochem Biophys* 2023;**737**:109553.
14. Palikaras K, Daskalaki I, Markaki M, Tavernarakis N. Mitophagy and age-related pathologies: development of new therapeutics by targeting mitochondrial turnover. *Pharmacol Ther* 2017;**178**:157−74.
15. Youle RJ, Narendra DP. Mechanisms of mitophagy. *Nat Rev Mol Cell Biol* 2011;**12**:9−14.
16. West AP, Khoury-Hanold W, Staron M, Tal MC, Pineda CM, Lang SM, et al. Mitochondrial DNA stress primes the antiviral innate immune response. *Nature* 2015;**520**:553−7.
17. Decout A, Katz JD, Venkatraman S, Ablasser A. The cGAS−STING pathway as a therapeutic target in inflammatory diseases. *Nat Rev Immunol* 2021;**21**:548−69.
18. Barber GN. STING: infection, inflammation and cancer. *Nat Rev Immunol* 2015;**15**:760−70.
19. Sliter DA, Martinez J, Hao L, Chen X, Sun N, Fischer TD, et al. Parkin and PINK1 mitigate STING-induced inflammation. *Nature* 2018;**561**:258−62.
20. Wu Y, Wei Q, Yu J. The cGAS/STING pathway: a sensor of senescence-associated DNA damage and trigger of inflammation in early age-related macular degeneration. *Clin Interv Aging* 2019;**14**:1277−83.
21. Wang S, Long H, Hou L, Feng B, Ma Z, Wu Y, et al. The mitophagy pathway and its implications in human diseases. *Signal Transduct Targeted Ther* 2023;**8**:304.
22. Wang X, Wang M, Cai M, Shao R, Xia G, Zhao W. Miriplatin-loaded liposome, as a novel mitophagy inducer, suppresses pancreatic cancer proliferation through blocking POLG and TFAM-mediated mtDNA replication. *Acta Pharm Sin B* 2023;**13**:4477−501.
23. Qiu WQ, Ai W, Zhu FD, Zhang Y, Guo MS, Law BY, et al. Polygala saponins inhibit NLRP3 inflammasome-mediated neuroinflammation *via* SHP-2-mediated mitophagy. *Free Radic Biol Med* 2022;**179**:76−94.
24. Naik E, Dixit VM. Mitochondrial reactive oxygen species drive proinflammatory cytokine production. *J Exp Med* 2011;**208**:417−20.
25. van Horssen J, van Schaik P, Witte M. Inflammation and mitochondrial dysfunction: a vicious circle in neurodegenerative disorders?. *Neurosci Lett* 2019;**710**:132931.
26. Ko TK, Tan DJY. Is disrupted mitophagy a central player to Parkinson's disease pathology?. *Cureus* 2023;**15**:e35458.
27. Barcelos IP, Troxell RM, Graves JS. Mitochondrial dysfunction and multiple sclerosis. *Biology (Basel)* 2019;**8**:37.
28. Chakravorty A, Jetto CT, Manjithaya R. Dysfunctional mitochondria and mitophagy as drivers of alzheimer's disease pathogenesis. *Front Aging Neurosci* 2019;**11**:311.
29. McBride HM, Neuspiel M, Wasiak S. Mitochondria: more than just a powerhouse. *Curr Biol* 2006;**16**:R551−60.
30. Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. *Cell* 2012;**148**:1145−59.

31. Austad SN, Ballinger S, Buford TW, Carter CS, Smith Jr DL, Darley-Usmar V, et al. Targeting whole body metabolism and mitochondrial bioenergetics in the drug development for Alzheimer's disease. *Acta Pharm Sin B* 2022;**12**:511−31.
32. Twig G, Elorza A, Molina AJ, Mohamed H, Wikstrom JD, Walzer G, et al. Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. *EMBO J* 2008;**27**:433−46.
33. Jin SM, Youle RJ. PINK1- and Parkin-mediated mitophagy at a glance. *J Cell Sci* 2012;**125**:795−9.
34. Scaini G, Mason BL, Diaz AP, Jha MK, Soares JC, Trivedi MH, et al. Dysregulation of mitochondrial dynamics, mitophagy and apoptosis in major depressive disorder: does inflammation play a role?. *Mol Psychiatr* 2022;**27**:1095−102.
35. Geisler S, Holmström KM, Skujat D, Fiesel FC, Rothfuss OC, Kahle PJ, et al. PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. *Nat Cell Biol* 2010;**12**:119−31.
36. Narendra DP, Jin SM, Tanaka A, Suen DF, Gautier CA, Shen J, et al. PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biol* 2010;**8**:e1000298.
37. Norat P, Soldozy S, Sokolowski JD, Gorick CM, Kumar JS, Chae Y, et al. Mitochondrial dysfunction in neurological disorders: exploring mitochondrial transplantation. *NPJ Regen Med* 2020;**5**:22.
38. Lazarou M, Sliter DA, Kane LA, Sarraf SA, Wang C, Burman JL, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature* 2015;**524**:309−14.
39. Okatsu K, Oka T, Iguchi M, Imamura K, Kosako H, Tani N, et al. PINK1 autophosphorylation upon membrane potential dissipation is essential for Parkin recruitment to damaged mitochondria. *Nat Commun* 2012;**3**:1016.
40. Gustafsson ÅB, Dorn 2nd GW. Evolving and expanding the roles of mitophagy as a homeostatic and pathogenic process. *Physiol Rev* 2019;**99**:853−92.
41. Luan Y, Luan Y, Feng Q, Chen X, Ren KD, Yang Y. Emerging role of mitophagy in the heart: therapeutic potentials to modulate mitophagy in cardiac diseases. *Oxid Med Cell Longev* 2021;**2021**:3259963.
42. Swerdlow NS, Wilkins HM. Mitophagy and the brain. *Int J Mol Sci* 2020;**21**:9661.
43. Sharma B, Pal D, Sharma U, Kumar A. Mitophagy: an emergence of new player in Alzheimer's disease. *Front Mol Neurosci* 2022;**15**: 921908.
44. Wang B, Abraham N, Gao G, Yang Q. Dysregulation of autophagy and mitochondrial function in Parkinson's disease. *Transl Neurodegener* 2016;**5**:19.
45. Zhang W, Xu C, Sun J, Shen HM, Wang J, Yang C. Impairment of the autophagy−lysosomal pathway in Alzheimer's diseases: pathogenic mechanisms and therapeutic potential. *Acta Pharm Sin B* 2022;**12**: 1019−40.
46. Shires SE, Gustafsson ÅB. Mitophagy and heart failure. *J Mol Med (Berl)* 2015;**93**:253−62.
47. Yang M, Linn BS, Zhang Y, Ren J. Mitophagy and mitochondrial integrity in cardiac ischemia−reperfusion injury. *Biochim Biophys Acta, Mol Basis Dis* 2019;**1865**:2293−302.
48. Harrington JS, Ryter SW, Plataki M, Price DR, Choi AMK. Mitochondria in health, disease, and aging. *Physiol Rev* 2023;**103**: 2349−422.
49. Onishi M, Yamano K, Sato M, Matsuda N, Okamoto K. Molecular mechanisms and physiological functions of mitophagy. *EMBO J* 2021;**40**:e104705.
50. Koyano F, Okatsu K, Kosako H, Tamura Y, Go E, Kimura M, et al. Ubiquitin is phosphorylated by PINK1 to activate parkin. *Nature* 2014;**510**:162−6.
51. Kane LA, Lazarou M, Fogel AI, Li Y, Yamano K, Sarraf SA, et al. PINK1 phosphorylates ubiquitin to activate Parkin E3 ubiquitin ligase activity. *J Cell Biol* 2014;**205**:143−53.
52. Wong YC, Holzbaur EL. Temporal dynamics of PARK2/parkin and OPTN/optineurin recruitment during the mitophagy of damaged mitochondria. *Autophagy* 2015;**11**:422−4.
53. Kataura T, Otten EG, Rabanal-Ruiz Y, Adriaenssens E, Urselli F, Scialo F, et al. NDP52 acts as a redox sensor in PINK1/Parkin-mediated mitophagy. *EMBO J* 2023;**42**:e111372.
54. Narendra DP, Youle RJ. Targeting mitochondrial dysfunction: role for PINK1 and Parkin in mitochondrial quality control. *Antioxidants Redox Signal* 2011;**14**:1929−38.
55. Killackey SA, Philpott DJ, Girardin SE. Mitophagy pathways in health and disease. *J Cell Biol* 2020;**219**:e202004029.
56. Mouton-Liger F, Jacoupy M, Corvol JC, Corti O. PINK1/Parkin-dependent mitochondrial surveillance: from pleiotropy to Parkinson's disease. *Front Mol Neurosci* 2017;**10**:120.
57. Imberechts D, Kinnart I, Wauters F, Terbeek J, Manders L, Wierda K, et al. DJ-1 is an essential downstream mediator in PINK1/parkin-dependent mitophagy. *Brain* 2022;**145**:4368−84.
58. Zheng T, Wang HY, Chen Y, Chen X, Wu ZL, Hu QY, et al. Src activation aggravates podocyte injury in diabetic nephropathy *via* suppression of FUNDC1-mediated mitophagy. *Front Pharmacol* 2022;**13**:897046.
59. Liu L, Li Y, Chen Q. The emerging role of FUNDC1-mediated mitophagy in cardiovascular diseases. *Front Physiol* 2021;**12**: 807654.
60. Xia J, Chu C, Li W, Chen H, Xie W, Cheng R, et al. Mitochondrial protein UCP1 inhibits the malignant behaviors of triple-negative breast cancer through activation of mitophagy and pyroptosis. *Int J Biol Sci* 2022;**18**:2949−61.
61. Zheng H, Zhu H, Liu X, Huang X, Huang A, Huang Y. Mitophagy in diabetic cardiomyopathy: roles and mechanisms. *Front Cell Dev Biol* 2021;**9**:750382.
62. Du J, Li J. The role of Wnt signaling pathway in atherosclerosis and its relationship with angiogenesis. *Exp Ther Med* 2018;**16**: 1975−81.
63. Manukjan N, Ahmed Z, Fulton D, Blankesteijn WM, Foulquier S. A systematic review of WNT signaling in endothelial cell oligodendrocyte interactions: potential relevance to cerebral small vessel disease. *Cells* 2020;**9**:1545.
64. Fang Z, Han X, Chen Y, Tong X, Xue Y, Yao S, et al. Oxidative stress-triggered Wnt signaling perturbation characterizes the tipping point of lung adeno-to-squamous transdifferentiation. *Signal Transduct Targeted Ther* 2023;**8**:16.
65. Teleanu DM, Niculescu AG, Lungu II, Radu CI, Vladâcenco O, Roza E, et al. An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases. *Int J Mol Sci* 2022;**23**:5938.
66. Rehman MU, Sehar N, Dar NJ, Khan A, Arafah A, Rashid S, et al. Mitochondrial dysfunctions, oxidative stress and neuroinflammation as therapeutic targets for neurodegenerative diseases: an update on current advances and impediments. *Neurosci Biobehav Rev* 2023; **144**:104961.
67. Cheignon C, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, Collin F. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. *Redox Biol* 2018;**14**:450−64.
68. Scudamore O, Ciossek T. Increased oxidative stress exacerbates α-synuclein aggregation *in vivo*. *J Neuropathol Exp Neurol* 2018;**77**: 443−53.
69. Li Y, Xia X, Wang Y, Zheng JC. Mitochondrial dysfunction in microglia: a novel perspective for pathogenesis of Alzheimer's disease. *J Neuroinflammation* 2022;**19**:248.
70. Culmsee C, Michels S, Scheu S, Arolt V, Dannlowski U, Alferink J. Mitochondria, microglia, and the immune system-how are they linked in affective disorders?. *Front Psychiatr* 2018;**9**:739.
71. Fang EF, Hou Y, Palikaras K, Adriaanse BA, Kerr JS, Yang B, et al. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nat Neurosci* 2019;**22**:401−12.
72. Babcock AA, Ilkjær L, Clausen BH, Villadsen B, Dissing-Olesen L, Bendixen AT, et al. Cytokine-producing microglia have an altered beta-amyloid load in aged APP/PS1 Tg mice. *Brain Behav Immun* 2015;**48**:86−101.

73. Lucin KM, O'Brien CE, Bieri G, Czirr E, Mosher KI, Abbey RJ, et al. Microglial beclin 1 regulates retromer trafficking and phagocytosis and is impaired in Alzheimer's disease. *Neuron* 2013;**79**:873−86.
74. Houtman J, Freitag K, Gimber N, Schmoranzer J, Heppner FL, Jendrach M. Beclin1-driven autophagy modulates the inflammatory response of microglia *via* NLRP3. *EMBO J* 2019;**38**:e99430.
75. Wang D, Zhang J, Jiang W, Cao Z, Zhao F, Cai T, et al. The role of NLRP3−CASP1 in inflammasome-mediated neuroinflammation and autophagy dysfunction in manganese-induced, hippocampal-dependent impairment of learning and memory ability. *Autophagy* 2017;**13**:914−27.
76. Cen X, Chen Y, Xu X, Wu R, He F, Zhao Q, et al. Pharmacological targeting of MCL-1 promotes mitophagy and improves disease pathologies in an Alzheimer's disease mouse model. *Nat Commun* 2020;**11**:5731.
77. de Marañón AM, Díaz-Pozo P, Canet F, Díaz-Morales N, Abad-Jiménez Z, López-Domènech S, et al. Metformin modulates mitochondrial function and mitophagy in peripheral blood mononuclear cells from type 2 diabetic patients. *Redox Biol* 2022;**53**:102342.
78. Fang EF, Scheibye-Knudsen M, Brace LE, Kassahun H, SenGupta T, Nilsen H, et al. Defective mitophagy in XPA *via* PARP-1 hyperactivation and NAD^+/SIRT1 reduction. *Cell* 2014;**157**:882−96.
79. Hou Y, Lautrup S, Cordonnier S, Wang Y, Croteau DL, Zavala E, et al. NAD^+ supplementation normalizes key Alzheimer's features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency. *Proc Natl Acad Sci U S A* 2018;**115**:E1876−85.
80. Ou Z, Kong X, Sun X, He X, Zhang L, Gong Z, et al. Metformin treatment prevents amyloid plaque deposition and memory impairment in APP/PS1 mice. *Brain Behav Immun* 2018;**69**:351−63.
81. Hong Y, Liu Y, Yu D, Wang M, Hou Y. The neuroprotection of progesterone against Aβ-induced NLRP3−Caspase-1 inflammasome activation *via* enhancing autophagy in astrocytes. *Int Immunopharm* 2019;**74**:105669.
82. Hong Y, Liu Y, Zhang G, Wu H, Hou Y. Progesterone suppresses Aβ_{42}-induced neuroinflammation by enhancing autophagy in astrocytes. *Int Immunopharm* 2018;**54**:336−43.
83. Hu ZL, Sun T, Lu M, Ding JH, Du RH, Hu G. Kir6.1/K-ATP channel on astrocytes protects against dopaminergic neurodegeneration in the MPTP mouse model of Parkinson's disease *via* promoting mitophagy. *Brain Behav Immun* 2019;**81**:509−22.
84. Chen J, Mao K, Yu H, Wen Y, She H, Zhang H, et al. p38-TFEB pathways promote microglia activation through inhibiting CMA-mediated NLRP3 degradation in Parkinson's disease. *J Neuroinflammation* 2021;**18**:295.
85. Tu HY, Yuan BS, Hou XO, Zhang XJ, Pei CS, Ma YT, et al. α-Synuclein suppresses microglial autophagy and promotes neurodegeneration in a mouse model of Parkinson's disease. *Aging Cell* 2021;**20**:e13522.
86. Qin Y, Qiu J, Wang P, Liu J, Zhao Y, Jiang F, et al. Impaired autophagy in microglia aggravates dopaminergic neurodegeneration by regulating NLRP3 inflammasome activation in experimental models of Parkinson's disease. *Brain Behav Immun* 2021;**91**:324−38.
87. Cheng J, Liao Y, Dong Y, Hu H, Yang N, Kong X, et al. Microglial autophagy defect causes Parkinson disease-like symptoms by accelerating inflammasome activation in mice. *Autophagy* 2020;**16**:2193−205.
88. Ahmed S, Kwatra M, Ranjan Panda S, Murty USN, Naidu VGM. Andrographolide suppresses NLRP3 inflammasome activation in microglia through induction of parkin-mediated mitophagy in *in-vitro* and *in-vivo* models of Parkinson disease. *Brain Behav Immun* 2021;**91**:142−58.
89. Qiu J, Chen Y, Zhuo J, Zhang L, Liu J, Wang B, et al. Urolithin A promotes mitophagy and suppresses NLRP3 inflammasome activation in lipopolysaccharide-induced BV2 microglial cells and MPTP-induced Parkinson's disease model. *Neuropharmacology* 2022;**207**:108963.
90. Han X, Sun S, Sun Y, Song Q, Zhu J, Song N, et al. Small molecule-driven NLRP3 inflammation inhibition *via* interplay between ubiquitination and autophagy: implications for Parkinson disease. *Autophagy* 2019;**15**:1860−81.
91. Han X, Xu T, Fang Q, Zhang H, Yue L, Hu G, et al. Quercetin hinders microglial activation to alleviate neurotoxicity *via* the interplay between NLRP3 inflammasome and mitophagy. *Redox Biol* 2021;**44**:102010.
92. Deng Z, Dong Y, Zhou X, Lu JH, Yue Z. Pharmacological modulation of autophagy for Alzheimer's disease therapy: opportunities and obstacles. *Acta Pharm Sin B* 2022;**12**:1688−706.
93. Wu AG, Pan R, Law BY, Qiu WQ, Wu JM, He CL, et al. Targeting autophagy as a therapeutic strategy for identification of liganans from *Peristrophe japonica* in Parkinson's disease. *Signal Transduct Targeted Ther* 2021;**6**:67.
94. Cho MH, Cho K, Kang HJ, Jeon EY, Kim HS, Kwon HJ, et al. Autophagy in microglia degrades extracellular β-amyloid fibrils and regulates the NLRP3 inflammasome. *Autophagy* 2014;**10**:1761−75.
95. Sharma M, Rajendrarao S, Shahani N, Ramírez-Jarquín UN, Subramaniam S. Cyclic GMP-AMP synthase promotes the inflammatory and autophagy responses in Huntington disease. *Proc Natl Acad Sci U S A* 2020;**117**:15989−99.
96. Banerjee P, Mehta AR, Nirujogi RS, Cooper J, James OG, Nanda J, et al. Cell-autonomous immune dysfunction driven by disrupted autophagy in C9orf72-ALS iPSC-derived microglia contributes to neurodegeneration. *Sci Adv* 2023;**9**:eabq0651.
97. Debye B, Schmülling L, Zhou L, Rune G, Beyer C, Johann S. Neurodegeneration and NLRP3 inflammasome expression in the anterior thalamus of SOD1(G93A) ALS mice. *Brain Pathol* 2018;**28**:14−27.
98. Sun M, Gong P, Yuan B, Liu N, Li X, Zhang W, et al. AXL-induced autophagy mitigates experimental autoimmune encephalomyelitis by suppressing microglial inflammation *via* the PI3K/AKT/mTOR signaling pathway. *Mol Immunol* 2023;**159**:15−27.
99. Shao BZ, Ke P, Xu ZQ, Wei W, Cheng MH, Han BZ, et al. Autophagy plays an important role in anti-inflammatory mechanisms stimulated by Alpha7 nicotinic acetylcholine receptor. *Front Immunol* 2017;**8**:553.
100. Shao BZ, Wei W, Ke P, Xu ZQ, Zhou JX, Liu C. Activating cannabinoid receptor 2 alleviates pathogenesis of experimental autoimmune encephalomyelitis *via* activation of autophagy and inhibiting NLRP3 inflammasome. *CNS Neurosci Ther* 2014;**20**:1021−8.
101. Su SH, Wu YF, Lin Q, Wang DP, Hai J. URB597 protects against NLRP3 inflammasome activation by inhibiting autophagy dysfunction in a rat model of chronic cerebral hypoperfusion. *J Neuroinflammation* 2019;**16**:260.
102. He Q, Li Z, Wang Y, Hou Y, Li L, Zhao J. Resveratrol alleviates cerebral ischemia/reperfusion injury in rats by inhibiting NLRP3 inflammasome activation through Sirt1-dependent autophagy induction. *Int Immunopharm* 2017;**50**:208−15.
103. Wang Y, Meng C, Zhang J, Wu J, Zhao J. Inhibition of GSK-3β alleviates cerebral ischemia/reperfusion injury in rats by suppressing NLRP3 inflammasome activation through autophagy. *Int Immunopharm* 2019;**68**:234−41.
104. Geng J, Liu J, Yuan X, Liu W, Guo W. Andrographolide triggers autophagy-mediated inflammation inhibition and attenuates chronic unpredictable mild stress (CUMS)-induced depressive-like behavior in mice. *Toxicol Appl Pharmacol* 2019;**379**:114688.
105. Cao S, Shrestha S, Li J, Yu X, Chen J, Yan F, et al. Melatonin-mediated mitophagy protects against early brain injury after subarachnoid hemorrhage through inhibition of NLRP3 inflammasome activation. *Sci Rep* 2017;**7**:2417.
106. Oduro PK, Zheng X, Wei J, Yang Y, Wang Y, Zhang H, et al. The cGAS−STING signaling in cardiovascular and metabolic diseases:

future novel target option for pharmacotherapy. *Acta Pharm Sin B* 2022;**12**:50−75.
107. Chen Z, Meng C, Mai J, Liu Y, Li H, Shen H. An mRNA vaccine elicits STING-dependent antitumor immune responses. *Acta Pharm Sin B* 2023;**13**:1274−86.
108. Ma X, Xin D, She R, Liu D, Ge J, Mei Z. Novel insight into cGAS−STING pathway in ischemic stroke: from pre- to post-disease. *Front Immunol* 2023;**14**:1275408.
109. Ma Z, Damania B. The cGAS−STING defense pathway and its counteraction by viruses. *Cell Host Microbe* 2016;**19**:150−8.
110. Paul BD, Snyder SH, Bohr VA. Signaling by cGAS−STING in neurodegeneration, neuroinflammation, and aging. *Trends Neurosci* 2021;**44**:83−96.
111. Fryer AL, Abdullah A, Taylor JM, Crack PJ. The complexity of the cGAS−STING pathway in CNS pathologies. *Front Neurosci* 2021; **15**:621501.
112. Hu Y, Chen Y, Liu T, Zhu C, Wan L, Yao W. The bidirectional roles of the cGAS−STING pathway in pain processing: cellular and molecular mechanisms. *Biomed Pharmacother* 2023;**163**:114869.
113. Wu X, Yu N, Ye Z, Gu Y, Zhang C, Chen M, et al. Inhibition of cGAS−STING pathway alleviates neuroinflammation-induced retinal ganglion cell death after ischemia/reperfusion injury. *Cell Death Dis* 2023;**14**:615.
114. Diamond MS, Kanneganti TD. Innate immunity: the first line of defense against SARS-CoV-2. *Nat Immunol* 2022;**23**:165−76.
115. Zheng W, Liu A, Xia N, Chen N, Meurens F, Zhu J. How the innate immune DNA sensing cGAS−STING pathway is involved in apoptosis. *Int J Mol Sci* 2023;**24**:3029.
116. Murthy AMV, Robinson N, Kumar S. Crosstalk between cGAS−STING signaling and cell death. *Cell Death Differ* 2020;**27**: 2989−3003.
117. Roh JS, Sohn DH. Damage-associated molecular patterns in inflammatory diseases. *Immune Netw* 2018;**18**:e27.
118. Nastasi C, Mannarino L, D'Incalci M. DNA damage response and immune defense. *Int J Mol Sci* 2020;**21**:7504.
119. Unterholzner L, Dunphy G. cGAS-independent STING activation in response to DNA damage. *Mol Cell Oncol* 2019;**6**:1558682.
120. Chen Q, Sun L, Chen ZJ. Regulation and function of the cGAS−STING pathway of cytosolic DNA sensing. *Nat Immunol* 2016;**17**:1142−9.
121. Li X, Shu C, Yi G, Chaton CT, Shelton CL, Diao J, et al. Cyclic GMP−AMP synthase is activated by double-stranded DNA-induced oligomerization. *Immunity* 2013;**39**:1019−31.
122. Shu C, Li X, Li P. The mechanism of double-stranded DNA sensing through the cGAS−STING pathway. *Cytokine Growth Factor Rev* 2014;**25**:641−8.
123. Zhou W, Whiteley AT, Kranzusch PJ. Analysis of human cGAS activity and structure. *Methods Enzymol* 2019;**625**:13−40.
124. Hansen AL, Brandtoft AM, Nyegaard M, Thielke AL, Olagnier D, Holm CK. Global transcriptional changes in response to cGAMP depend on STING in human THP-1 cells. *Cell Mol Immunol* 2018;**15**: 983−5.
125. Smith JA. STING, the endoplasmic reticulum, and mitochondria: is three a crowd or a conversation?. *Front Immunol* 2020;**11**:611347.
126. Bai J, Liu F. The cGAS−cGAMP−STING pathway: a molecular link between immunity and metabolism. *Diabetes* 2019;**68**: 1099−108.
127. Flood BA, Higgs EF, Li S, Luke JJ, Gajewski TF. STING pathway agonism as a cancer therapeutic. *Immunol Rev* 2019;**290**:24−38.
128. Vila IK, Chamma H, Steer A, Saccas M, Taffoni C, Turtoi E, et al. STING orchestrates the crosstalk between polyunsaturated fatty acid metabolism and inflammatory responses. *Cell Metabol* 2022;**34**:125-39.e8.
129. Yum S, Li M, Fang Y, Chen ZJ. TBK1 recruitment to STING activates both IRF3 and NF-κB that mediate immune defense against tumors and viral infections. *Proc Natl Acad Sci U S A* 2021;**118**: e2100225118.
130. Ni J, Guo T, Zhou Y, Jiang S, Zhang L, Zhu Z. STING signaling activation modulates macrophage polarization *via* CCL2 in radiation-induced lung injury. *J Transl Med* 2023;**21**:590.
131. Kuhl N, Linder A, Philipp N, Nixdorf D, Fischer H, Veth S, et al. STING agonism turns human T cells into interferon-producing cells but impedes their functionality. *EMBO Rep* 2023;**24**:e55536.
132. Feng Z, Liao X, Peng J, Quan J, Zhang H, Huang Z, et al. PCSK9 causes inflammation and cGAS/STING pathway activation in diabetic nephropathy. *FASEB J* 2023;**37**:e23127.
133. Wang D, Zhao H, Shen Y, Chen Q. A variety of nucleic acid species are sensed by cGAS, implications for its diverse functions. *Front Immunol* 2022;**13**:826880.
134. Xiong Y, Leng Y, Tian H, Deng X, Li W, Li W, et al. Decreased MFN2 activates the cGAS−STING pathway in diabetic myocardial ischaemia-reperfusion by triggering the release of mitochondrial DNA. *Cell Commun Signal* 2023;**21**:192.
135. Slavik KM, Kranzusch PJ. CBASS to cGAS−STING: the origins and mechanisms of nucleotide second messenger immune signaling. *Annu Rev Virol* 2023;**10**:423−53.
136. Gulla A, Morelli E, Samur MK, Botta C, Hideshima T, Bianchi G, et al. Bortezomib induces anti-multiple myeloma immune response mediated by cGAS/STING pathway activation. *Blood Cancer Discov* 2021;**2**:468−83.
137. Zhang C, Shang G, Gui X, Zhang X, Bai XC, Chen ZJ. Structural basis of STING binding with and phosphorylation by TBK1. *Nature* 2019;**567**:394−8.
138. Liu X, Wei L, Xu F, Zhao F, Huang Y, Fan Z, et al. SARS-CoV-2 spike protein-induced cell fusion activates the cGAS−STING pathway and the interferon response. *Sci Signal* 2022;**15**:eabg8744.
139. Liu N, Pang X, Zhang H, Ji P. The cGAS−STING pathway in bacterial infection and bacterial immunity. *Front Immunol* 2021;**12**:814709.
140. Hoong BYD, Gan YH, Liu H, Chen ES. cGAS−STING pathway in oncogenesis and cancer therapeutics. *Oncotarget* 2020;**11**:2930−55.
141. Griffith JW, Sokol CL, Luster AD. Chemokines and chemokine receptors: positioning cells for host defense and immunity. *Annu Rev Immunol* 2014;**32**:659−702.
142. Sierawska O, Małkowska P, Taskin C, Hrynkiewicz R, Mertowska P, Grywalska E, et al. Innate immune system response to burn damage—focus on cytokine alteration. *Int J Mol Sci* 2022;**23**:716.
143. Wan D, Jiang W, Hao J. Research advances in how the cGAS−STING pathway controls the cellular inflammatory response. *Front Immunol* 2020;**11**:615.
144. Jiang M, Chen P, Wang L, Li W, Chen B, Liu Y, et al. cGAS−STING, an important pathway in cancer immunotherapy. *J Hematol Oncol* 2020;**13**:81.
145. Quraishe S, Forbes LH, Andrews MR. The extracellular environment of the CNS: influence on plasticity, sprouting, and axonal regeneration after spinal cord injury. *Neural Plast* 2018;**2018**:2952386.
146. Guo M, Zhu F, Qiu W, Qiao G, Law BY, Yu L, et al. High-throughput screening for amyloid-β binding natural small-molecules based on the combinational use of biolayer interferometry and UHPLC−DAD-Q/TOF-MS/MS. *Acta Pharm Sin B* 2022;**12**:1723−39.
147. Xie X, Ma G, Li X, Zhao J, Zhao Z, Zeng J. Activation of innate immune cGAS−STING pathway contributes to Alzheimer's pathogenesis in 5×FAD mice. *Nat Aging* 2023;**3**:202−12.
148. Jin M, Shiwaku H, Tanaka H, Obita T, Ohuchi S, Yoshioka Y, et al. Tau activates microglia *via* the PQBP1−cGAS−STING pathway to promote brain inflammation. *Nat Commun* 2021;**12**:6565.
149. Roy ER, Wang B, Wan YW, Chiu G, Cole A, Yin Z, et al. Type I interferon response drives neuroinflammation and synapse loss in Alzheimer disease. *J Clin Invest* 2020;**130**:1912−30.
150. Wu Z, Tang W, Ibrahim F, Chen X, Yan H, Tao C, et al. Aβ induces neuroinflammation and microglial M1 polarization *via* cGAS−STING−IFITM3 signaling pathway in BV-2 cells. *Neurochem Res* 2023;**48**:2881−94.
151. Fruhwürth S, Reinert LS, Öberg C, Sakr M, Henricsson M, Zetterberg H, et al. TREM2 is down-regulated by HSV1 in microglia

and involved in antiviral defense in the brain. *Sci Adv* 2023;**9**: eadf5808.
152. Hinkle JT, Patel J, Panicker N, Karuppagounder SS, Biswas D, Belingon B, et al. STING mediates neurodegeneration and neuroinflammation in nigrostriatal α-synucleinopathy. *Proc Natl Acad Sci U S A* 2022;**119**:e2118819119.
153. Ma C, Liu Y, Li S, Ma C, Huang J, Wen S, et al. Microglial cGAS drives neuroinflammation in the MPTP mouse models of Parkinson's disease. *CNS Neurosci Ther* 2023;**29**:2018−35.
154. Szego EM, Malz L, Bernhardt N, Rösen-Wolff A, Falkenburger BH, Luksch H. Constitutively active STING causes neuroinflammation and degeneration of dopaminergic neurons in mice. *Elife* 2022;**11**: e81943.
155. Yu CH, Davidson S, Harapas CR, Hilton JB, Mlodzianoski MJ, Laohamonthonkul P, et al. TDP-43 triggers mitochondrial DNA release *via* mPTP to activate cGAS/STING in ALS. *Cell* 2020;**183**: 636-49.e18.
156. McCauley ME, O'Rourke JG, Yáñez A, Markman JL, Ho R, Wang X, et al. C9orf72 in myeloid cells suppresses STING-induced inflammation. *Nature* 2020;**585**:96−101.
157. Tan HY, Yong YK, Xue YC, Liu H, Furihata T, Shankar EM, et al. cGAS and DDX41-STING mediated intrinsic immunity spreads intercellularly to promote neuroinflammation in SOD1 ALS model. *iScience* 2022;**25**:104404.
158. Mathur V, Burai R, Vest RT, Bonanno LN, Lehallier B, Zardeneta ME, et al. Activation of the STING-dependent type I interferon response reduces microglial reactivity and neuroinflammation. *Neuron* 2017;**96**:1290-302.e6.
159. Li Q, Cao Y, Dang C, Han B, Han R, Ma H, et al. Inhibition of double-strand DNA-sensing cGAS ameliorates brain injury after ischemic stroke. *EMBO Mol Med* 2020;**12**:e11002.
160. Liao Y, Cheng J, Kong X, Li S, Li X, Zhang M, et al. HDAC3 inhibition ameliorates ischemia/reperfusion-induced brain injury by regulating the microglial cGAS−STING pathway. *Theranostics* 2020;**10**:9644−62.
161. Fritsch LE, Ju J, Gudenschwager Basso EK, Soliman E, Paul S, Chen J, et al. Type I interferon response is mediated by NLRX1−cGAS−STING signaling in brain injury. *Front Mol Neurosci* 2022;**15**:852243.
162. Li W, Shen N, Kong L, Huang H, Wang X, Zhang Y, et al. STING mediates microglial pyroptosis *via* interaction with NLRP3 in cerebral ischaemic stroke. *Stroke Vasc Neurol* 2023. Available from: https://doi.org/10.1136/svn-2023-002320.
163. Gulen MF, Samson N, Keller A, Schwabenland M, Liu C, Glück S, et al. cGAS−STING drives ageing-related inflammation and neurodegeneration. *Nature* 2023;**620**:374−80.
164. Nazmi A, Field RH, Griffin EW, Haugh O, Hennessy E, Cox D, et al. Chronic neurodegeneration induces type I interferon synthesis *via* STING, shaping microglial phenotype and accelerating disease progression. *Glia* 2019;**67**:1254−76.
165. Kerur N, Fukuda S, Banerjee D, Kim Y, Fu D, Apicella I, et al. cGAS drives noncanonical-inflammasome activation in age-related macular degeneration. *Nat Med* 2018;**24**:50−61.
166. Abdullah A, Zhang M, Frugier T, Bedoui S, Taylor JM, Crack PJ. STING-mediated type-I interferons contribute to the neuroinflammatory process and detrimental effects following traumatic brain injury. *J Neuroinflammation* 2018;**15**:323.
167. Reinert LS, Lopušná K, Winther H, Sun C, Thomsen MK, Nandakumar R, et al. Sensing of HSV-1 by the cGAS−STING pathway in microglia orchestrates antiviral defence in the CNS. *Nat Commun* 2016;**7**:13348.
168. Ding R, Li H, Liu Y, Ou W, Zhang X, Chai H, et al. Activating cGAS−STING axis contributes to neuroinflammation in CVST mouse model and induces inflammasome activation and microglia pyroptosis. *J Neuroinflammation* 2022;**19**: 137.
169. Wu W, Zhang X, Wang S, Li T, Hao Q, Li S, et al. Pharmacological inhibition of the cGAS−STING signaling pathway suppresses microglial M1-polarization in the spinal cord and attenuates neuropathic pain. *Neuropharmacology* 2022;**217**:109206.
170. Elzinga SE, Koubek EJ, Hayes JM, Carter A, Mendelson FE, Webber-Davis I, et al. Modeling the innate inflammatory cGAS/STING pathway: sexually dimorphic effects on microglia and cognition in obesity and prediabetes. *Front Cell Neurosci* 2023;**17**:1167688.
171. He S, Li X, Mittra N, Bhattacharjee A, Wang H, Zhao S, et al. Microglial cGAS deletion protects against amyloid-β induced Alzheimer's disease pathogenesis. *bioRxiv* 2023. Available from: https://doi.org/10.1101/2023.08.07.552300.
172. Reinert LS, Rashidi AS, Tran DN, Katzilieris-Petras G, Hvidt AK, Gohr M, et al. Brain immune cells undergo cGAS/STING-dependent apoptosis during herpes simplex virus type 1 infection to limit type I IFN production. *J Clin Invest* 2021;**131**:e136824.
173. Jeong GU, Lee S, Kim DY, Lyu J, Yoon GY, Kim KD, et al. Zika virus infection induces interleukin-1β-mediated inflammatory responses by macrophages in the brain of an adult mouse model. *J Virol* 2023;**97**:e0055623.
174. Patrycy M, Chodkowski M, Krzyzowska M. Role of microglia in herpesvirus-related neuroinflammation and neurodegeneration. *Pathogens* 2022;**11**:809.
175. Ni G, Ma Z, Damania B. cGAS and STING: at the intersection of DNA and RNA virus-sensing networks. *PLoS Pathog* 2018;**14**: e1007148.
176. Benarroch E. What is the role of the cytosolic DNA response in neurodegeneration?. *Neurology* 2021;**96**:940−3.
177. Maximova OA, Sturdevant DE, Kash JC, Kanakabandi K, Xiao Y, Minai M, et al. Virus infection of the CNS disrupts the immune-neural-synaptic axis *via* induction of pleiotropic gene regulation of host responses. *Elife* 2021;**10**:e62273.
178. Barkhane Z, Elmadi J, Satish Kumar L, Pugalenthi LS, Ahmad M, Reddy S. Multiple sclerosis and autoimmunity: a veiled relationship. *Cureus* 2022;**14**:e24294.
179. Masanneck L, Eichler S, Vogelsang A, Korsen M, Wiendl H, Budde T, et al. The STING−IFN-β-dependent axis is markedly low in patients with relapsing-remitting multiple sclerosis. *Int J Mol Sci* 2020;**21**:9249.
180. Gomes AP, Blenis J. A nexus for cellular homeostasis: the interplay between metabolic and signal transduction pathways. *Curr Opin Biotechnol* 2015;**34**:110−7.
181. Moehlman AT, Kanfer G, Youle RJ. Loss of STING in parkin mutant flies suppresses muscle defects and mitochondria damage. *PLoS Genet* 2023;**19**:e1010828.
182. Zhong W, Rao Z, Xu J, Sun Y, Hu H, Wang P, et al. Defective mitophagy in aged macrophages promotes mitochondrial DNA cytosolic leakage to activate STING signaling during liver sterile inflammation. *Aging Cell* 2022;**21**:e13622.
183. Li MZ, Dai XY, Zhao YX, Li XW, Zhao Y, Li JL. Lycopene attenuates di(2-ethylhexyl) phthalate-induced mitochondrial damage and inflammation in kidney *via* cGAS−STING signaling. *J Agric Food Chem* 2023;**71**:569−79.
184. Tan HWS, Lu G, Dong H, Cho YL, Natalia A, Wang L, et al. A degradative to secretory autophagy switch mediates mitochondria clearance in the absence of the mATG8-conjugation machinery. *Nat Commun* 2022;**13**:3720.
185. Druzhyna NM, Wilson GL, LeDoux SP. Mitochondrial DNA repair in aging and disease. *Mech Ageing Dev* 2008;**129**:383−90.
186. Wang W, Zhao F, Ma X, Perry G, Zhu X. Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances. *Mol Neurodegener* 2020;**15**:30.
187. Zhang W, Li G, Luo R, Lei J, Song Y, Wang B, et al. Cytosolic escape of mitochondrial DNA triggers cGAS−STING−NLRP3 axis-dependent nucleus pulposus cell pyroptosis. *Exp Mol Med* 2022;**54**: 129−42.
188. Dabravolski SA, Nikiforov NG, Zhuravlev AD, Orekhov NA, Grechko AV, Orekhov AN. Role of the mtDNA mutations and mitophagy in inflammaging. *Int J Mol Sci* 2022;**23**:1323.

189. Chen G, Kroemer G, Kepp O. Mitophagy: an emerging role in aging and age-associated diseases. *Front Cell Dev Biol* 2020;**8**:200.
190. Liu J, Liu W, Li R, Yang H. Mitophagy in Parkinson's disease: from pathogenesis to treatment. *Cells* 2019;**8**:712.
191. Deas E, Wood NW, Plun-Favreau H. Mitophagy and Parkinson's disease: the PINK1−parkin link. *Biochim Biophys Acta* 2011;**1813**: 623−33.
192. Wen X, Tang L, Zhong R, Liu L, Chen L, Zhang H. Role of mitophagy in regulating intestinal oxidative damage. *Antioxidants (Basel)* 2023;**12**:480.
193. He B, Yu H, Liu S, Wan H, Fu S, Liu S, et al. Mitochondrial cristae architecture protects against mtDNA release and inflammation. *Cell Rep* 2022;**41**:111774.
194. Yue L, Yao H. Mitochondrial dysfunction in inflammatory responses and cellular senescence: pathogenesis and pharmacological targets for chronic lung diseases. *Br J Pharmacol* 2016;**173**: 2305−18.
195. Mani S, Swargiary G, Chadha R. Mitophagy impairment in neurodegenerative diseases: pathogenesis and therapeutic interventions. *Mitochondrion* 2021;**57**:270−93.
196. Zhao Y, Liu B, Xu L, Yu S, Fu J, Wang J, et al. ROS-induced mtDNA release: the emerging messenger for communication between neurons and innate immune cells during neurodegenerative disorder progression. *Antioxidants* 2021;**10**:1917.
197. Standaert DG, Childers GM. Alpha-synuclein-mediated DNA damage, STING activation, and neuroinflammation in Parkinson's disease. *Proc Natl Acad Sci U S A* 2022;**119**:e2204058119.
198. Kausar S, Yang L, Abbas MN, Hu X, Zhao Y, Zhu Y, et al. Mitochondrial DNA: a key regulator of anti-microbial innate immunity. *Genes (Basel)* 2020;**11**:379.
199. Ferecskó AS, Smallwood MJ, Moore A, Liddle C, Newcombe J, Holley J, et al. STING-triggered CNS inflammation in human neurodegenerative diseases. *Biomedicines* 2023;**11**:1375.
200. Talbot EJ, Joshi L, Thornton P, Dezfouli M, Tsafou K, Perkinton M, et al. The cGAS−STING pathway regulates microglial chemotaxis in genome instability. *Nucleic Acids Res* 2023;**52**:1188−206.
201. Wang WY, Tan MS, Yu JT, Tan L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Ann Transl Med* 2015;**3**:136.
202. Lawrence JM, Schardien K, Wigdahl B, Nonnemacher MR. Roles of neuropathology-associated reactive astrocytes: a systematic review. *Acta Neuropathol Commun* 2023;**11**:42.
203. Tjalkens RB, Popichak KA, Kirkley KA. Inflammatory activation of microglia and astrocytes in manganese neurotoxicity. *Adv Neurobiol* 2017;**18**:159−81.
204. Rocha DN, Ferraz-Nogueira JP, Barrias CC, Relvas JB, Pêgo AP. Extracellular environment contribution to astrogliosis-lessons learned from a tissue engineered 3D model of the glial scar. *Front Cell Neurosci* 2015;**9**:377.
205. Mottahedin A, Ardalan M, Chumak T, Riebe I, Ek J, Mallard C. Effect of neuroinflammation on synaptic organization and function in the developing brain: implications for neurodevelopmental and neurodegenerative disorders. *Front Cell Neurosci* 2017;**11**:190.
206. Lenz M, Eichler A, Vlachos A. Monitoring and modulating inflammation-associated alterations in synaptic plasticity: role of brain stimulation and the blood−brain interface. *Biomolecules* 2021; **11**:359.
207. Schäffer M, Beiter T, Becker HD, Hunt TK. Neuropeptides: mediators of inflammation and tissue repair?. *Arch Surg* 1998;**133**: 1107−16.
208. Bauer IE, Pascoe MC, Wollenhaupt-Aguiar B, Kapczinski F, Soares JC. Inflammatory mediators of cognitive impairment in bipolar disorder. *J Psychiatr Res* 2014;**56**:18−27.
209. Chakrabarty T, Torres IJ, Bond DJ, Yatham LN. Inflammatory cytokines and cognitive functioning in early-stage bipolar I disorder. *J Affect Disord* 2019;**245**:679−85.
210. Harrison NA, Cercignani M, Voon V, Critchley HD. Effects of inflammation on hippocampus and substantia nigra responses to novelty in healthy human participants. *Neuropsychopharmacology* 2015;**40**:831−8.
211. Milde S, van Tartwijk FW, Vilalta A, Hornik TC, Dundee JM, Puigdellívol M, et al. Inflammatory neuronal loss in the substantia nigra induced by systemic lipopolysaccharide is prevented by knockout of the $P2Y_6$ receptor in mice. *J Neuroinflammation* 2021; **18**:225.
212. Gatto CL, Broadie K. Genetic controls balancing excitatory and inhibitory synaptogenesis in neurodevelopmental disorder models. *Front Synaptic Neurosci* 2010;**2**:4.
213. Breitinger U, Breitinger HG. Excitatory and inhibitory neuronal signaling in inflammatory and diabetic neuropathic pain. *Mol Med* 2023;**29**:53.
214. Xiong R, Zhou XG, Tang Y, Wu JM, Sun YS, Teng JF, et al. Lychee seed polyphenol protects the blood−brain barrier through inhibiting $A\beta_{25-35}$-induced NLRP3 inflammasome activation *via* the AMPK/mTOR/ULK1-mediated autophagy in bEnd.3 cells and APP/PS1 mice. *Phytother Res* 2021;**35**:954−73.
215. Galea I. The blood−brain barrier in systemic infection and inflammation. *Cell Mol Immunol* 2021;**18**:2489−501.
216. Li Y, Zhu ZY, Huang TT, Zhou YX, Wang X, Yang LQ, et al. The peripheral immune response after stroke-A double edge sword for blood−brain barrier integrity. *CNS Neurosci Ther* 2018;**24**:1115−28.
217. Kadry H, Noorani B, Cucullo L. A blood−brain barrier overview on structure, function, impairment, and biomarkers of integrity. *Fluids Barriers CNS* 2020;**17**:69.
218. Udeochu JC, Amin S, Huang Y, Fan L, Torres ERS, Carling GK, et al. Tau activation of microglial cGAS−IFN reduces MEF2C-mediated cognitive resilience. *Nat Neurosci* 2023;**26**:737−50.
219. Zou M, Ke Q, Nie Q, Qi R, Zhu X, Liu W, et al. Inhibition of cGAS−STING by JQ1 alleviates oxidative stress-induced retina inflammation and degeneration. *Cell Death Differ* 2022;**29**:1816−33.
220. Chin AC. Neuroinflammation and the cGAS−STING pathway. *J Neurophysiol* 2019;**121**:1087−91.
221. Wang Y, Wei B, Wang D, Wu J, Gao J, Zhong H, et al. DNA damage repair promotion in colonic epithelial cells by andrographolide downregulated cGAS−STING pathway activation and contributed to the relief of CPT-11-induced intestinal mucositis. *Acta Pharm Sin B* 2022;**12**:262−73.
222. Kang J, Wu J, Liu Q, Wu X, Zhao Y, Ren J. Post-Translational Modifications of STING: a potential therapeutic target. *Front Immunol* 2022;**13**:888147.
223. Hirschenberger M, Lepelley A, Rupp U, Klute S, Hunszinger V, Koepke L, et al. ARF1 prevents aberrant type I interferon induction by regulating STING activation and recycling. *Nat Commun* 2023; **14**:6770.
224. Hansen AL, Mukai K, Schopfer FJ, Taguchi T, Holm CK. STING palmitoylation as a therapeutic target. *Cell Mol Immunol* 2019;**16**: 236−41.
225. Liu D, Wu H, Wang C, Li Y, Tian H, Siraj S, et al. STING directly activates autophagy to tune the innate immune response. *Cell Death Differ* 2019;**26**:1735−49.
226. Burman JL, Pickles S, Wang C, Sekine S, Vargas JNS, Zhang Z, et al. Mitochondrial fission facilitates the selective mitophagy of protein aggregates. *J Cell Biol* 2017;**216**:3231−47.
227. Zhang Q, Wei J, Liu Z, Huang X, Sun M, Lai W, et al. STING signaling sensing of DRP1-dependent mtDNA release in kupffer cells contributes to lipopolysaccharide-induced liver injury in mice. *Redox Biol* 2022;**54**:102367.
228. Kim IS, Silwal P, Jo EK. Mitofusin 2, a key coordinator between mitochondrial dynamics and innate immunity. *Virulence* 2021;**12**: 2273−84.
229. Li C, Liu J, Hou W, Kang R, Tang D. STING1 promotes ferroptosis through MFN1/2-dependent mitochondrial fusion. *Front Cell Dev Biol* 2021;**9**:698679.

230. Su CI, Kao YT, Chang CC, Chang Y, Ho TS, Sun HS, et al. DNA-induced 2′3′-cGAMP enhances haplotype-specific human STING cleavage by dengue protease. *Proc Natl Acad Sci U S A* 2020;**117**:15947−54.
231. Youle RJ, van der Bliek AM. Mitochondrial fission, fusion, and stress. *Science* 2012;**337**:1062−5.
232. Moehlman AT, Youle RJ. Mitochondrial quality control and restraining innate immunity. *Annu Rev Cell Dev Biol* 2020;**36**:265−89.
233. Zhang K, Wang S, Gou H, Zhang J, Li C. Crosstalk between autophagy and the cGAS−STING signaling pathway in type I interferon production. *Front Cell Dev Biol* 2021;**9**:748485.
234. Casadio M. Lysosomal disorder boosts STING. *Nat Cell Biol* 2021;**23**:927.
235. Hopfner KP, Hornung V. Molecular mechanisms and cellular functions of cGAS−STING signalling. *Nat Rev Mol Cell Biol* 2020;**21**:501−21.
236. Liang Q, Seo GJ, Choi YJ, Kwak MJ, Ge J, Rodgers MA, et al. Crosstalk between the cGAS DNA sensor and Beclin-1 autophagy protein shapes innate antimicrobial immune responses. *Cell Host Microbe* 2014;**15**:228−38.
237. Wang S, Wang L, Qin X, Turdi S, Sun D, Culver B, et al. ALDH2 contributes to melatonin-induced protection against APP/PS1 mutation-prompted cardiac anomalies through cGAS−-STING−TBK1-mediated regulation of mitophagy. *Signal Transduct Targeted Ther* 2020;**5**:119.
238. Hasan M, Gonugunta VK, Dobbs N, Ali A, Palchik G, Calvaruso MA, et al. Chronic innate immune activation of TBK1 suppresses mTORC1 activity and dysregulates cellular metabolism. *Proc Natl Acad Sci U S A* 2017;**114**:746−51.
239. Liu Y, Chen X, Zhao Y, Wang XY, Luo YW, Chen L, et al. Small cytosolic double-stranded DNA represses cyclic GMP−AMP synthase activation and induces autophagy. *Cell Rep* 2023;**42**:112852.
240. Klein B, Reynolds MB, Xu B, Gharaee-Kermani M, Gao Y, Berthier CC, et al. Epidermal ZBP1 stabilizes mitochondrial Z-DNA to drive UV-induced IFN signaling in autoimmune photosensitivity. *bioRxiv* 2024. Available from: https://doi.org/10.1101/2024.01.23.576771.
241. Wileman T. Autophagy as a defence against intracellular pathogens. *Essays Biochem* 2013;**55**:153−63.
242. Hou Y, Wei Y, Lautrup S, Yang B, Wang Y, Cordonnier S, et al. NAD^+ supplementation reduces neuroinflammation and cell senescence in a transgenic mouse model of Alzheimer's disease *via* cGAS−STING. *Proc Natl Acad Sci U S A* 2021;**118**:e2011226118.
243. Zhou G, Wang X, Guo M, Qu C, Gao L, Yu J, et al. Mitophagy deficiency activates stimulator of interferon genes activation and aggravates pathogenetic cardiac remodeling. *Genes Dis* 2023. Available from: https://doi.org/10.1016/j.gendis.2023.08.003.
244. Han C, Qian X, Ren X, Zhang S, Hu L, Li J, et al. Inhibition of cGAS in paraventricular nucleus attenuates hypertensive heart injury *via* regulating microglial autophagy. *Mol Neurobiol* 2022;**59**:7006−24.
245. Jiménez-Loygorri JI, Villarejo-Zori B, Viedma-Poyatos Á, Zapata-Muñoz J, Benítez-Fernández R, Frutos-Lisón MD, et al. Mitophagy curtails cytosolic mtDNA-dependent activation of cGAS/STING inflammation during aging. *Nat Commun* 2024;**15**:830.
246. Kwon OC, Song JJ, Yang Y, Kim SH, Kim JY, Seok MJ, et al. SGK1 inhibition in glia ameliorates pathologies and symptoms in Parkinson disease animal models. *EMBO Mol Med* 2021;**13**:e13076.
247. de Oliveira LG, Angelo YS, Iglesias AH, Peron JPS. Unraveling the link between mitochondrial dynamics and neuroinflammation. *Front Immunol* 2021;**12**:624919.
248. Xue T, Ji J, Sun Y, Huang X, Cai Z, Yang J, et al. Sphingosine-1-phosphate, a novel TREM2 ligand, promotes microglial phagocytosis to protect against ischemic brain injury. *Acta Pharm Sin B* 2022;**12**:1885−98.
249. Larrick JW, Mendelsohn AR. Modulation of cGAS−STING pathway by nicotinamide riboside in Alzheimer's disease. *Rejuvenation Res* 2021;**24**:397−402.
250. Chen C, Chen Y, Liu T, Song D, Ma D, Cheng O. Dexmedetomidine can enhance PINK1/Parkin-mediated mitophagy in MPTP-induced PD mice model by activating AMPK. *Oxid Med Cell Longev* 2022;**2022**:7511393.
251. Masaldan S, Callegari S, Dewson G. Therapeutic targeting of mitophagy in Parkinson's disease. *Biochem Soc Trans* 2022;**50**:783−97.
252. O'Callaghan B, Hardy J, Plun-Favreau H. PINK1: from Parkinson's disease to mitophagy and back again. *PLoS Biol* 2023;**21**:e3002196.
253. Sun X, Duan Y, Qin C, Li JC, Duan G, Deng X, et al. Distinct multilevel misregulations of Parkin and PINK1 revealed in cell and animal models of TDP-43 proteinopathy. *Cell Death Dis* 2018;**9**:953.
254. Khalil B, El Fissi N, Aouane A, Cabirol-Pol MJ, Rival T, Liévens JC. PINK1-induced mitophagy promotes neuroprotection in Huntington's disease. *Cell Death Dis* 2015;**6**:e1617.
255. Quinn PMJ, Moreira PI, Ambrósio AF, Alves CH. PINK1/PARKIN signalling in neurodegeneration and neuroinflammation. *Acta Neuropathol Commun* 2020;**8**:189.
256. Heo JM, Ordureau A, Paulo JA, Rinehart J, Harper JW. The PINK1−PARKIN mitochondrial ubiquitylation pathway drives a program of OPTN/NDP52 recruitment and TBK1 activation to promote mitophagy. *Mol Cell* 2015;**60**:7−20.
257. Liu Y, Duan R, Li P, Zhang B, Liu Y. 3-*N*-Butylphthalide attenuates neuroinflammation in rotenone-induced Parkinson's disease models *via* the cGAS−STING pathway. *Int J Immunopathol Pharmacol* 2024;**38**:3946320241229041.
258. Pinti M, Ferraro D, Nasi M. Microglia activation: a role for mitochondrial DNA?. *Neural Regen Res* 2021;**16**:2393−4.
259. Wu AG, Zhou XG, Qiao G, Yu L, Tang Y, Yan L, et al. Targeting microglial autophagic degradation in NLRP3 inflammasome-mediated neurodegenerative diseases. *Ageing Res Rev* 2021;**65**:101202.
260. Wang Z, Wang Q, Li S, Li XJ, Yang W, He D. Microglial autophagy in Alzheimer's disease and Parkinson's disease. *Front Aging Neurosci* 2022;**14**:1065183.
261. Rango M, Bresolin N. Brain mitochondria, aging, and Parkinson's disease. *Genes (Basel)* 2018;**9**:250.
262. Rossi G, Salvi E, Benussi L, Mehmeti E, Geviti A, Bellini S, et al. The PINK1 p.Asn521Thr variant is associated with earlier disease onset in GRN/C9orf72 frontotemporal lobar degeneration. *Int J Mol Sci* 2022;**23**:12847.
263. Liu X, Cheng R, Verbitsky M, Kisselev S, Browne A, Mejia-Sanatana H, et al. Genome-wide association study identifies candidate genes for Parkinson's disease in an Ashkenazi Jewish population. *BMC Med Genet* 2011;**12**:104.
264. Lai D, Alipanahi B, Fontanillas P, Schwantes-An TH, Aasly J, Alcalay RN, et al. Genomewide association studies of LRRK2 modifiers of Parkinson's disease. *Ann Neurol* 2021;**90**:76−88.
265. Pankratz N, Wilk JB, Latourelle JC, DeStefano AL, Halter C, Pugh EW, et al. Genomewide association study for susceptibility genes contributing to familial Parkinson disease. *Hum Genet* 2009;**124**:593−605.
266. López-Cáceres A, Cruz-Sanabria F, Mayorga P, Sanchez AI, Gonzalez-Nieves S, Ayala-Ramírez P, et al. Association between risk polymorphisms for neurodegenerative diseases and cognition in colombian patients with frontotemporal dementia. *Front Neurol* 2022;**13**:675301.
267. Ying C, Kang P, Binkley MM, Ford AL, Chen Y, Hassenstab J, et al. Neuroinflammation and amyloid deposition in the progression of mixed Alzheimer and vascular dementia. *Neuroimage Clin* 2023;**38**:103373.
268. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: current evidence and future directions. *Alzheimers Dement* 2016;**12**:719−32.
269. Kim TK, Bae EJ, Jung BC, Choi M, Shin SJ, Park SJ, et al. Inflammation promotes synucleinopathy propagation. *Exp Mol Med* 2022;**54**:2148−61.
270. Espinosa-Oliva AM, Ruiz R, Soto MS, Boza-Serrano A, Rodriguez-Perez AI, Roca-Ceballos MA, et al. Inflammatory bowel disease

induces pathological α-synuclein aggregation in the human gut and brain. *Neuropathol Appl Neurobiol* 2024;**50**:e12962.
271. Hong Z, Mei J, Guo H, Zhu J, Wang C. Intervention of cGAS−STING signaling in sterile inflammatory diseases. *J Mol Cell Biol* 2022;**14**:mjac005.
272. Shao J, Meng Y, Yuan K, Wu Q, Zhu S, Li Y, et al. RU.521 mitigates subarachnoid hemorrhage-induced brain injury *via* regulating microglial polarization and neuroinflammation mediated by the cGAS/STING/NF-κB pathway. *Cell Commun Signal* 2023;**21**:264.
273. Thanan R, Oikawa S, Hiraku Y, Ohnishi S, Ma N, Pinlaor S, et al. Oxidative stress and its significant roles in neurodegenerative diseases and cancer. *Int J Mol Sci* 2014;**16**:193−217.
274. Singh A, Kukreti R, Saso L, Kukreti S. Oxidative stress: a key modulator in neurodegenerative diseases. *Molecules* 2019;**24**:1583.
275. Miller AH. Norman Cousins Lecture. Mechanisms of cytokine-induced behavioral changes: psychoneuroimmunology at the translational interface. *Brain Behav Immun* 2009;**23**:149−58.
276. Bruno A, Dolcetti E, Rizzo FR, Fresegna D, Musella A, Gentile A, et al. Inflammation-associated synaptic alterations as shared threads in depression and multiple sclerosis. *Front Cell Neurosci* 2020;**14**:169.
277. Chung WS, Welsh CA, Barres BA, Stevens B. Do glia drive synaptic and cognitive impairment in disease?. *Nat Neurosci* 2015;**18**:1539−45.
278. Shankar GM, Walsh DM. Alzheimer's disease: synaptic dysfunction and Abeta. *Mol Neurodegener* 2009;**4**:48.
279. Kraft AD, Harry GJ. Features of microglia and neuroinflammation relevant to environmental exposure and neurotoxicity. *Int J Environ Res Publ Health* 2011;**8**:2980−3018.
280. Carson MJ, Thrash JC, Walter B. The cellular response in neuroinflammation: the role of leukocytes, microglia and astrocytes in neuronal death and survival. *Clin Neurosci Res* 2006;**6**:237−45.
281. Boyd RJ, Avramopoulos D, Jantzie LL, McCallion AS. Neuroinflammation represents a common theme amongst genetic and environmental risk factors for Alzheimer and Parkinson diseases. *J Neuroinflammation* 2022;**19**:223.
282. Ashrafi G, Schwarz TL. The pathways of mitophagy for quality control and clearance of mitochondria. *Cell Death Differ* 2013;**20**:31−42.
283. Shen X, Sun P, Zhang H, Yang H. Mitochondrial quality control in the brain: the physiological and pathological roles. *Front Neurosci* 2022;**16**:1075141.
284. Kshirsagar S, Sawant N, Morton H, Reddy AP, Reddy PH. Mitophagy enhancers against phosphorylated Tau-induced mitochondrial and synaptic toxicities in Alzheimer disease. *Pharmacol Res* 2021;**174**:105973.
285. Kshirsagar S, Sawant N, Morton H, Reddy AP, Reddy PH. Protective effects of mitophagy enhancers against amyloid beta-induced mitochondrial and synaptic toxicities in Alzheimer disease. *Hum Mol Genet* 2022;**31**:423−39.
286. Fan L, Zhaohong X, Xiangxue W, Yingying X, Xiao Z, Xiaoyan Z, et al. Melatonin ameliorates the progression of Alzheimer's disease by inducing TFEB nuclear translocation, promoting mitophagy, and regulating NLRP3 inflammasome activity. *BioMed Res Int* 2022;**2022**:8099459.
287. Wang H, Fu J, Xu X, Yang Z, Zhang T. Rapamycin activates mitophagy and alleviates cognitive and synaptic plasticity deficits in a mouse model of Alzheimer's disease. *J Gerontol A Biol Sci Med Sci* 2021;**76**:1707−13.
288. Li Q, Zhang T, Wang J, Zhang Z, Zhai Y, Yang GY, et al. Rapamycin attenuates mitochondrial dysfunction *via* activation of mitophagy in experimental ischemic stroke. *Biochem Biophys Res Commun* 2014;**444**:182−8.
289. Li Q, Gao S, Kang Z, Zhang M, Zhao X, Zhai Y, et al. Rapamycin enhances mitophagy and attenuates apoptosis after spinal ischemia−reperfusion injury. *Front Neurosci* 2018;**12**:865.
290. Wang H, Jiang T, Li W, Gao N, Zhang T. Resveratrol attenuates oxidative damage through activating mitophagy in an *in vitro* model of Alzheimer's disease. *Toxicol Lett* 2018;**282**:100−8.
291. Ye M, Wu H, Li S. Resveratrol alleviates oxygen/glucose deprivation/reoxygenation-induced neuronal damage through induction of mitophagy. *Mol Med Rep* 2021;**23**:73.
292. Wang WW, Han R, He HJ, Li J, Chen SY, Gu Y, et al. Administration of quercetin improves mitochondria quality control and protects the neurons in 6-OHDA-lesioned Parkinson's disease models. *Aging (Albany NY)* 2021;**13**:11738−51.
293. Qiu WQ, Yu L, He CL, Wu JM, Law BY, Yu CL, et al. Two 18-norspirostane steroidal saponins as novel mitophagy enhancers improve Alzheimer's disease. *Clin Transl Med* 2023;**13**:e1390.
294. Wu AG, Yong YY, He CL, Li YP, Zhou XY, Yu L, et al. Novel 18-norspirostane steroidal saponins: extending lifespan and mitigating neurodegeneration through promotion of mitophagy and mitochondrial biogenesis in *Caenorhabditis elegans*. *Mech Ageing Dev* 2024;**218**:111901.
295. Xie C, Zhuang XX, Niu Z, Ai R, Lautrup S, Zheng S, et al. Amelioration of Alzheimer's disease pathology by mitophagy inducers identified *via* machine learning and a cross-species workflow. *Nat Biomed Eng* 2022;**6**:76−93.
296. Wiser C, Kim B, Vincent J, Ascano M. Small molecule inhibition of human cGAS reduces total cGAMP output and cytokine expression in cells. *Sci Rep* 2020;**10**:7604.
297. Pan Y, You Y, Sun L, Sui Q, Liu L, Yuan H, et al. The STING antagonist H-151 ameliorates psoriasis *via* suppression of STING/NF-κB-mediated inflammation. *Br J Pharmacol* 2021;**178**:4907−22.
298. Kobritz M, Borjas T, Patel V, Coppa G, Aziz M, Wang P. H151, A small molecule inhibitor of sting as a novel therapeutic in intestinal ischemia−reperfusion injury. *Shock* 2022;**58**:241−50.
299. Ahmad L, Zhang SY, Casanova JL, Sancho-Shimizu V. Human TBK1: a gatekeeper of neuroinflammation. *Trends Mol Med* 2016;**22**:511−27.
300. Oakes JA, Davies MC, Collins MO. TBK1: a new player in ALS linking autophagy and neuroinflammation. *Mol Brain* 2017;**10**:5.
301. Tarassishin L, Suh HS, Lee SC. Interferon regulatory factor 3 plays an anti-inflammatory role in microglia by activating the PI3K/Akt pathway. *J Neuroinflammation* 2011;**8**:187.
302. Martín-Maestro P, Sproul A, Martinez H, Paquet D, Gerges M, Noggle S, et al. Autophagy induction by bexarotene promotes mitophagy in presenilin 1 familial Alzheimer's disease iPSC-derived neural stem cells. *Mol Neurobiol* 2019;**56**:8220−36.
303. Han Y, Wang N, Kang J, Fang Y. β-Asarone improves learning and memory in $A\beta_{1-42}$-induced Alzheimer's disease rats by regulating PINK1−Parkin-mediated mitophagy. *Metab Brain Dis* 2020;**35**:1109−17.
304. Yang X, Zhang M, Dai Y, Sun Y, Aman Y, Xu Y, et al. Spermidine inhibits neurodegeneration and delays aging *via* the PINK1−PDR1-dependent mitophagy pathway in *C. elegans*. *Aging (Albany NY)* 2020;**12**:16852−66.
305. Bertram L, Tanzi RE. The genetic epidemiology of neurodegenerative disease. *J Clin Invest* 2005;**115**:1449−57.
306. Knox EG, Aburto MR, Clarke G, Cryan JF, O'Driscoll CM. The blood−brain barrier in aging and neurodegeneration. *Mol Psychiatr* 2022;**27**:2659−73.
307. Pardridge WM. Drug transport across the blood−brain barrier. *J Cerebr Blood Flow Metabol* 2012;**32**:1959−72.
308. Banks WA. Characteristics of compounds that cross the blood−brain barrier. *BMC Neurol* 2009;**9**(Suppl 1):S3.
309. Hersh DS, Wadajkar AS, Roberts N, Perez JG, Connolly NP, Frenkel V, et al. Evolving drug delivery strategies to overcome the blood brain barrier. *Curr Pharmaceut Des* 2016;**22**:1177−93.
310. Pandey M, Jain N, Kanoujia J, Hussain Z, Gorain B. Advances and challenges in intranasal delivery of antipsychotic agents targeting the central nervous system. *Front Pharmacol* 2022;**13**:865590.

311. D'Amico RS, Aghi MK, Vogelbaum MA, Bruce JN. Convection-enhanced drug delivery for glioblastoma: a review. *J Neuro Oncol* 2021;**151**:415−27.
312. Hersh AM, Alomari S, Tyler BM. Crossing the blood−brain barrier: advances in nanoparticle technology for drug delivery in neuro-oncology. *Int J Mol Sci* 2022;**23**:4153.
313. Skopelja-Gardner S, An J, Elkon KB. Role of the cGAS−STING pathway in systemic and organ-specific diseases. *Nat Rev Nephrol* 2022;**18**:558−72.
314. Guerini D. STING agonists/antagonists: their potential as therapeutics and future developments. *Cells* 2022;**11**:1159.
315. Raj N, Fernandes S, Charyulu NR, Dubey A, G SR, Hebbar S. Postmarket surveillance: a review on key aspects and measures on the effective functioning in the context of the United Kingdom and Canada. *Ther Adv Drug Saf* 2019;**10**: 2042098619865413.
316. Roden DM, Wilke RA, Kroemer HK, Stein CM. Pharmacogenomics: the genetics of variable drug responses. *Circulation* 2011;**123**: 1661−70.
317. Ahmed S, Zhou Z, Zhou J, Chen SQ. Pharmacogenomics of drug metabolizing enzymes and transporters: relevance to precision medicine. *Dev Reprod Biol* 2016;**14**:298−313.
318. Brothers KB, Rothstein MA. Ethical, legal and social implications of incorporating personalized medicine into healthcare. *Per Med* 2015; **12**:43−51.
319. Wei J, Mu J, Tang Y, Qin D, Duan J, Wu A. Next-generation nanomaterials: advancing ocular anti-inflammatory drug therapy. *J Nanobiotechnol* 2023;**21**:282.
320. Zhu FD, Hu YJ, Yu L, Zhou XG, Wu JM, Tang Y, et al. Nanoparticles: a hope for the treatment of inflammation in CNS. *Front Pharmacol* 2021;**12**:683935.
321. Mi Z, Yao Q, Qi Y, Zheng J, Liu J, Liu Z, et al. Salmonella-mediated blood−brain barrier penetration, tumor homing and tumor microenvironment regulation for enhanced chemo/bacterial glioma therapy. *Acta Pharm Sin B* 2023;**13**:819−33.
322. Ahlawat J, Guillama Barroso G, Masoudi Asil S, Alvarado M, Armendariz I, Bernal J, et al. Nanocarriers as potential drug delivery candidates for overcoming the blood−brain barrier: challenges and possibilities. *ACS Omega* 2020;**5**:12583−95.
323. Palle S, Neerati P. Improved neuroprotective effect of resveratrol nanoparticles as evinced by abrogation of rotenone-induced behavioral deficits and oxidative and mitochondrial dysfunctions in rat model of Parkinson's disease. *Naunyn-Schmiedeberg's Arch Pharmacol* 2018;**391**:445−53.
324. Han Y, Chu X, Cui L, Fu S, Gao C, Li Y, et al. Neuronal mitochondria-targeted therapy for Alzheimer's disease by systemic delivery of resveratrol using dual-modified novel biomimetic nanosystems. *Drug Deliv* 2020;**27**:502−18.
325. Rajput A, Bariya A, Allam A, Othman S, Butani SB. *In situ* nanostructured hydrogel of resveratrol for brain targeting: *in vitro−in vivo* characterization. *Drug Deliv Transl Res* 2018;**8**:1460−70.
326. Lu Q, Chen R, Du S, Chen C, Pan Y, Luan X, et al. Activation of the cGAS−STING pathway combined with CRISPR-Cas9 gene editing triggering long-term immunotherapy. *Biomaterials* 2022;**291**: 121871.
327. Mary A, Eysert F, Checler F, Chami M. Mitophagy in Alzheimer's disease: molecular defects and therapeutic approaches. *Mol Psychiatr* 2023;**28**:202−16.
328. Paul A, Collins MG, Lee HY. Gene therapy: the next-generation therapeutics and their delivery approaches for neurological disorders. *Front Genome Ed* 2022;**4**:899209.
329. de Kock R, Borne BVD, Soud MY, Belderbos H, Stege G, de Saegher M, et al. Circulating biomarkers for monitoring therapy response and detection of disease progression in lung cancer patients. *Cancer Treat Res Commun* 2021;**28**:100410.
330. Podlesniy P, Llorens F, Puigròs M, Serra N, Sepúlveda-Falla D, Schmidt C, et al. Cerebrospinal fluid mitochondrial DNA in rapid and slow progressive forms of Alzheimer's disease. *Int J Mol Sci* 2020; **21**:6298.
331. Zhao X, Moore DL. Neural stem cells: developmental mechanisms and disease modeling. *Cell Tissue Res* 2018;**371**:1−6.
332. Ruan H, Li Y, Wang C, Jiang Y, Han Y, Li Y, et al. Click chemistry extracellular vesicle/peptide/chemokine nanocarriers for treating central nervous system injuries. *Acta Pharm Sin B* 2023;**13**: 2202−18.
333. Wang X, Ma S, Yang B, Huang T, Meng N, Xu L, et al. Resveratrol promotes hUC-MSCs engraftment and neural repair in a mouse model of Alzheimer's disease. *Behav Brain Res* 2018;**339**:297−304.