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REVIEW ARTICLE

cGAS-STING-mediated IFN-I Response in Host Defense and Neuro-inflammatory Diseases

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Abstract: The presence of foreign or misplaced nucleic acids is a dangerous signal that triggers innate immune responses by activating cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) and binding to its downstream signaling effector stimulator of interferon genes (STING). Then the cGAS-STING pathway activation links nucleic acid-sensing to immune responses and pathogenic entities clearance. However, the overactivation of this signaling pathway leads to fatal immune disorders and contributes to the progression of many human inflammatory diseases. Therefore, optimal activation of this pathway is crucial for the elimination of invading pathogens and the maintenance of immune homeostasis. In this review, we will summarize its fundamental roles in initiating host defense against invading pathogens and discuss its pathogenic roles in multiple neuro-inflammatory diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and other neurodegenerative diseases.

Keywords: cGAS, STING, neuroinflammation, AD, PD, HD, ALS, MS.

1. INTRODUCTION

In the innate immune system, pattern recognition receptors (PRRs) recognize foreign products, pathogen or damage-associated molecular patterns (PAMPs and DAMPs, often generated from our own cells) to activate the production of type I interferons (IFN-I) and other cytokines that are essential for the effective host defense [1-3], but the molecular mechanism of recognition remains elusive. Over the past two decades, the seminal discovery of mammalian cytosolic DNA sensor cGAS and identification of its downstream signaling effector STING has expanded our understanding of nucleic acids recognition [4-7]. When foreign DNA (derived from bacterial or viral infection) or self DNA (leakage from the nucleus or mitochondria under some pathological conditions) is sensed, the cGAS-STING pathway links nucleic acid-sensing to immune response [8, 9]. The dimeric cGAS protein binds to double-stranded DNA (dsDNA) and catalyzes the formation of cyclic guanosine monophosphate adenosine monophosphate (cGAMP), a diffusible cyclic dinucleotide that activates the Endoplasmic-Reticulum (ER) resident membrane protein STING (also known as TMEM173 [10], MPYS [11], MITA [12] and ERIS [13]) [14, 15]. Activated STING then traffics from the endoplasmic reticulum (ER) to an ER-Golgi intermediate compartment (ERGIC) and recruits tank-binding kinase 1(TBK1) and IκB kinase (IKK), which phosphorylate the transcription factor interferon (IFN) regulatory factor 3 (IRF3) and the nuclear factor-κB (NF-κB) inhibitor IκBα, respectively. Phosphorylated IRF3 dimerizes, translocates to the nucleus and induces the production of interferons (IFNs). Meanwhile, phosphorylated IκBα induces the translocation of NF-κB to the nucleus and activates the transcription of several inflammatory cytokines such as TNF, IL-1β and IL-6 [14, 16].

IFN-I's are principal antiviral molecules of the innate immune system and associated with varied immunomodulatory functions of host defense; thus cGAS-STING pathway-triggered IFN-I production and innate immune response play crucial roles in host defense against invading pathogens, while aberrant IFN-I overproduction can lead to IFN-I-driven immune disorders and diseases [17, 18]. In what contexts does the cGAS-STING pathway-triggered IFN-I production is good or bad for cells? In this review, we discuss

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Table 1. Summary of studies that implicated the STING-dependent IFN-I response in neuro-inflammatory diseases.

Disease Name	Study Models	Conclusion	Refs.
Alzheimer's disease	*In-vivo* mouse model *In-vitro* cell culture	Deletion of the IFN-I receptor in APP/PS1 mice preserves cognitive function	[25]
Alzheimer's disease	*In-vivo* mouse model *In-vitro* cell culture	IFN-I signaling mediates neuro -inflammatory events in Alzheimer's disease	[26]
Alzheimer's disease	*In-vivo* mouse model	The CP of J20 mice displayed an overall overexpression of IFN-I response genes	[27]
Parkinson's disease	*In-vivo* mouse model	IFNs contribute to the neuroinflammatory response and disease progression	[28]
Parkinson's disease	*In-vivo* mouse model	Parkin and PINK1 mitigate STING-induced inflammation	[29]
Multiple sclerosis	Clinical patients	Aligned expression of IFI16 and STING genes in RRMS patients' blood	[30]
Multiple sclerosis	*In-vivo* mouse model	Activation of STING-dependent IFN-I response reduces neuroinflammation	[23]
Multiple sclerosis	*In-vitro* cell culture	BBI suppresses autoimmune neuroinflammation via STING/IFN-β axis	[31]
Amyotrophic lateral sclerosis	*In-vivo* mouse model Patient cells	Blocking STING prevents inflammation-related damage in ALS	[32]
Amyotrophic lateral sclerosis	*In-vivo* mouse model *In-vitro* cell culture	Blocking STING suppresses hyperactive IFN-I responses	[33]
Huntington's disease	*In-vitro* cell culture	Depletion of cGAS decreases the expression of inflammatory genes	[34]
Huntington's disease	*In-vivo* mouse model *In-vitro* cell culture	cGAS-STING mediated inflammatory response in HD	[35]

the protective effects of the cGAS-STING pathway in bacterial and viral infections and its deleterious roles in multiple neuro-inflammatory diseases.

2. INVOLVEMENT OF THE CGAS-STING PATHWAY-TRIGGERED IFN-I RESPONSE IN ANTIBACTERIAL AND ANTIVIRAL IMMUNITY

Several studies have implicated the crucial role of the cGAS-STING pathway in antibacterial defense. Ramya and colleagues found that Listeria monocytogenes infection activated IFN-I expression in a STING-TBK1-dependent manner, and Listeria monocytogenes-infected STING deficient mouse embryonic fibroblasts (MEFs) failed to stimulate *Ifnb* and *Ifna4* mRNA expression. In the same study, they also observed similar results during Francisella tularensis and Legionella pneumophila infection [19]. Another study reported that the cGAS-STING pathway was activated and promoted IFN-I expression during Mycobacterium Bovis infection, and the cytokine secretions were significantly reduced in the sicGAS group [20]. Similarly, Nanthapon *et al.* demonstrated *in vivo* that cGAS-STING-induced IFN-I expression contributes to the clearing of nontuberculous mycobacteria (NTM) infection [21]. Taken together, these findings demonstrate the essential role of the cGAS-STING pathway for innate immune responses to clear bacterial entities.

Simultaneously, growing evidence implicates the protective roles of the cGAS-STING pathway in antiviral immunity. Wuertz and colleagues described that the cGAS-STING pathway is required for host defense against neuropathological West Nile virus (WNV) infection; STING deficient mice displayed increased viral load and virus dissemination in the central nervous system (CNS) [22]. These findings demonstrate the neuroprotective role of STING in WNV infection. Another study reported that functional STING is necessary for ganciclovir (GCV) to induce IFN-I response and reduce neuroinflammation in cultured myeloid cells and in a mouse model of MS [23]. Moreover, a recent study reported that herpes simplex virus 1 (HSV-1)-infected microglia confer cGAS-STING-dependent antiviral activities and IFN-I production, and mice lacking cGAS or STING are highly susceptible to HSV-1 infection [25]. Another similar research indicated that inhibition of the cGAS-STING pathway attenuates HSV-1-induced innate antiviral immune responses and promotes HSV-1 replication [24]. Overall, these findings strongly suggest the protective effects of cGAS-STING-mediated IFN-I response in host defense, and targeting this pathway could be a new therapeutic approach to enhance innate immune responses.

3. STING-DEPENDENT IFN-I RESPONSE IN NEURO-INFLAMMATORY DISEASES

The cGAS-STING pathway responds not only to foreign DNA (viral, bacterial) but also to self-DNA (damaged DNA, mitochondrial DNA), as observed in multiple neuro-inflammatory diseases (Table **1**) [25-35]. In the following text, we discuss the pathogenic roles of this cGAS/STING-dependent IFN-I response in each one of these diseases.

3.1. Alzheimer's Disease

Alzheimer's Disease (AD) is the most common neuro-degenerative disease and is characterized by the extracellular accumulation of senile plaques containing amyloid-beta (Aβ) deposits and the presence of neurofibrillary tangles containing hyper-phosphorylated tau [36, 37]. Unfortunately, past research concerning Aβ and hyperphosphorylated tau has failed or produced little success in clinical appearances [38]. In addition to those two pathological hallmarks, a growing body of literature describes the neuroinflammation in brain tissue from AD patients and transgenic mouse models, which contributes to AD pathology [36, 39-41]. As the main cell type of innate immune system in the CNS, microglia activate the immune system and accumulate around Aβ plaques, thus playing an important role in the pathogenesis of AD. Furthermore, activated microglia and increased level of IL-1 in AD patients have been reported [42, 43]. As aging is the greatest risk factor for AD, previous studies have shown the deleterious role of IFN-I signaling in hippocampal neurogenesis and brain function in response to aging [44, 45]. Other evidence regarding the contribution of neuroinflammation in AD pathology includes that individuals administered non-steroidal anti-inflammatory drugs (NSAIDs) display a lower prevalence of AD compared to respective controls [46]; choroid plexus transcriptome revealed an overall overexpression of IFN-I response genes in a mouse model of Alzheimer's disease [27]. Taken together, these findings indicate that excessive cGAS/STING -mediated IFN-I production is linked to interferonopathies of AD, and alleviating IFN -I response-related neuroinflammation may slow the progression of this devastating disorder.

IFN-I signaling occurs through their cognate receptor (IFNAR), which is composed of two subunits IFNAR1 and IFNAR2 [47]. Minter *et al.* utilizing APP /PS1 x IFNAR1$^{-/-}$ mice, found that deletion of the type-1 interferon receptor in APP/PS1 mice improved memory defects and enhanced astrocyte reactivity but attenuated microgliosis surrounding amyloid deposition. In the same study, they also described that removal of IFNAR1 attenuates the IFN-I response and conditioned media from Aβ1-42-treated IFNAR1$^{-/-}$ primary glia was found to be less toxic to primary cultured neurons compared with the control media [25]. Another study demonstrated increased IFNα expression in APP/PS1 brains and pre-frontal cortex from AD patients, significantly; ablation of type-1 interferon-α receptor 1 expression in BE(2)M17 neuroblastoma cells, and primary neurons afforded protection against Aβ-induced toxicity [26]. In agreement with this, Minter MR and colleagues also reported that IRF3 or IRF7 knockdown (KD) cells were protected against Aβ-induced neurotoxicity compared to wildtype, which indicated the involvement of IFN-I signaling in response to Aβ [48]. Collectively, these findings strongly suggest that deletion of the IFN-I receptor prevents Aβ-induced neurotoxicity, and blocking cGAS/STING-dependent IFN-I response could help alleviate Aβ-induced neuronal cell death and cognitive decline in AD.

3.2. Parkinson's Disease

Parkinson's disease (PD) is a common age-related neuro-degenerative disease, which is accompanied by some motor dysfunction symptoms, such as resting tremor, muscle rigidity, and exercise reduction [49, 50]. Pathologically, the disease is characterized by the progressive loss of dopamine (DA) neurons in the substantia nigra pars compacta (SNpc) and deposition of Lewy bodies (LB), which consist of cytoplasmic inclusions of aggregated α-synuclein in a hyper-phosphorylated state [51]. Though the exact mechanism of PD is not entirely clear, neuroinflammation is considered a critical central event in the progression of this disease. Several studies have shown the increased neuroinflammation in patients and animal models of PD, including activated microglia and increased levels of numerous pro-inflammatory cytokines, which eventually lead to DA neuronal cell death [52, 53]. Accordingly, elevated IL6 plasma concentrations were linked to a higher risk of developing PD [54]. Since α-synuclein was the first risk factor unequivocally associated with a familial form of PD, Watson and coworkers studied the temporospatial distribution of microglial activation and the production of the proinflammatory cytokines in an α-synuclein transgenic mouse. Their study revealed an elevation in the number of Iba1^{+} reactive microglia and increased levels of TNFα in the SNpc of α-synuclein transgenic mice [55]. These findings further confirm the involvement of microglia activation and neuroinflammation events in the disease progression of PD. Moreover, the inhibition of the activation of microglial cells and inflammation effectively rescued the abnormalities in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine(MPTP)-induced PD mice [51], suggesting that the alleviation of neuroinflammation could be a therapeutic target for PD.

Previous studies have demonstrated that cGAS/STING-IFN-I signaling mediates neuroinflammation in PD pathology. Main *et al.* reported that IFN-I signaling is elevated in post mortem brain of PD patients and contributes to the neuroinflammatory response and disease progression in the MPTP mouse model of PD. More importantly, they demonstrated that the removal of IFN-I signaling either through genetic ablation of the IFNAR1 or treatment with a blocking monoclonal IFNAR1 antibody (MAR-1) reduced both the neuroinflammatory response and DA cell death induced by MPTP [28], providing direct evidence for the involvement of IFN-I signaling in PD. Consistent with this report, another study demonstrated that Parkin and PINK1 mitigate STING-induced inflammation; IFNAR1-blocking antibody treatment or STING deficiency rescued motor defect and dopaminergic neurons loss in the Prkn$^{-/-}$ mice [29], indicating cGAS/STING-dependent IFN-I signaling as a pivotal modulator of the early neuroinflammatory response and the DA cell death in disease progression of PD. To ascertain the source of DNA activating cGAS-STING pathway, Gao *et al.* reported mislocalization of genomic DNA as the trigger for cGAS-STING activation [56]. Moreover, Sliter *et al*. demonstrated that mitophagy and mitochondrial DNA can also trigger

cGAS-STING mediated neuroinflammation; they observed increased circulating mitochondrial DNA in $Prkn^{-/-}$ mice [29]. Therefore, further research is required on the mechanism for mitochondrial DNA leakage into the cytosol and potential clinical application for the intervention of this disease.

3.3. Huntington's Disease

Huntington's disease (HD) is an autosomal-dominant inherited neurodegenerative disorder caused by an expansion of CAG (cytosine-adenine-guanine) repeats in the gene *huntingtin* on chromosome 4 [57]. The main pathological hallmarks of this disease include neuronal loss in the striatum and cortex, motor and cognitive deficits, psychiatric disturbances [58], as well as microglial activation and dysregulation of the immune system [59]. Over the past years, inflammation has been implicated in the pathogenesis of HD; an elevated production of several pro-inflammatory cytokines (IL-6, IL-8, and TNF-α) and the impaired nuclear factor-kappa B (NF-κB) pathway (key participant in the inflammatory response) were observed in the brain of HD patients [60, 61]. Additionally, the presence of activated microglia and the increased number of microglia (a cellular indicator of inflammation) in the HD samples have also been reported [62, 63]. Furthermore, RNA sequence analysis of human HD patients revealed transcriptional dysregulation associated with pro-inflammatory pathway activation [64, 65]. All these results suggest that inflammation is involved in the disease pathophysiology of HD.

Additional studies have revealed the presence of numerous cytosolic and mitochondrial DNA, which are known to trigger the cGAS-STING pathway in postmortem striata of HD patients [35, 66]. In the same study, inflammation and activated cGAS/STING/IRF3 pathway have been reported. Importantly, cytosolic mitochondrial DNA activated the inflammatory response and the blockade of cGAS significantly inhibited the expression of INF-α and IFN-β, suggesting that the inflammation induced by cytosolic mitochondrial DNA in HD is mediated by cGAS /STING pathway [35]. In another study, Sharma *et al.* reported that cGAS is up-regulated and promotes the inflammatory responses in HD. Depletion of cGAS diminishes cGAS activity and decreases the expression of inflammatory genes in HD cells [34]. Collectively, these findings demonstrate that cGAS/STING mediated inflammation contributes to HD pathology and inhibition of cGAS/STING could help alleviate inflammation-related damage in HD.

3.4. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, is primarily characterized by the progressive degeneration of both upper motor neuron (UMN) and lower motor neuron (LMN), which leads to severe disability and eventual paralysis [67]. Although the mechanisms underlying the development of ALS remain poorly understood, numerous studies have shown the involvement of neuroinflammation in disease pathogenesis. The ALS-associated mutations of TDP-43 activate microglia and trigger NF-κB-mediated pathogenic pathways [68, 69]. Indeed, the blockade of NF-κB improved ALS disease symptoms in TDP-43 transgenic mice [69]. Wang *et al.* demonstrated IFN signaling pathway to be activated in an ALS mouse model, and reduction or deletion of IFNα receptor 1 inhibited IFN signaling and increased the lifespan of mice [70]. A variety of abnormal inflammatory cytokines have been consistently reported in ALS patients [71]. Therefore, neuroinflammation is an important mechanism for neuronal injury and ALS progression; inhibition of inflammatory response can help mitigate inflammation-related damage in ALS. However, the immune sensor proposed to trigger the inflammation observed in ALS remains unclear.

In a recent study, Yu *et al.* demonstrated that TDP-43 causes inflammation in ALS by triggering mitochondrial DNA release into the cytoplasm, which subsequently activates the cGAS-STING pathway. More importantly, genetic deletion or pharmacological inhibition of STING ameliorated disease in an ALS mouse model [32]. In another study, McCauley *et al.* showed that loss of C9orf72 induced inflammation mediated by the induction of IFN-I by STING, and blocking STING suppressed hyperactive IFN-I responses in $C9orf72^{-/-}$ mice [33]. Taken together, these findings indicate that cGAS-STING mediated inflammation contributes to the progression of ALS and targeting of this pathway may provide therapeutic benefits in this neuro-inflammatory disease.

3.5. Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder of the CNS and is characterized by the distribution of inflammatory lesions and loss of myelin, neuronal axons, and myelin-producing oligodendrocytes [72, 73]. Although the pathogenesis of MS is not clear, acute inflammatory lesions and their infiltration to the CNS play a crucial role in disease progression [74]. Recently, much focus has been given to IFN-I signaling as the mediator of CNS inflammation, contributing to pathogenesis. An *in vitro* model of axon injury showed the induction of IFN-I genes in microglia [75]; another *in vivo* model of axonal transection induced a robust IFN-I response, and lack of IFN-I signaling resulted in exaggerated cell infiltration in the injured area [76]. Future gene deletion analyses within the mouse model (autoimmune encephalomyelitis, (EAE)) revealed an IFN-I-dependent regulator of pro-inflammatory events in MS, and mice lacking either IFN-β or IFNAR develop more severe EAE [77, 78]. Similarly, Salem *et al.* reported that mice lacking transcription factors of IFN-I signaling develop more severe EAE, with increased CNS infiltration [79]. Taken together, these findings indicate the vital role of IFN-I signaling in the disease progression of MS, and the regulation of IFN production in the CNS is of importance.

Given that the induction of IFN-I is beneficial for MS, it may be critical for pharmacological intervention of the IFN-I signaling. IFNα and IFN-β, two members of the IFN-I family, have been used as an effective therapy for limiting lymphocyte infiltration in the brain and decreasing the relapse rate of the disease [80]. As an important upstream mediator of IFN-I signaling, STING is necessary for the beneficial treatment effects of IFN production in MS. Mathur *et al.* described that the FDA-approved antiviral drug ganciclovir (GCV) induces an IFN-I response and reduces neuroinflammation in a STING-dependent manner, and the STING-deficient mice lack these therapeutic effects [23]. Consistent

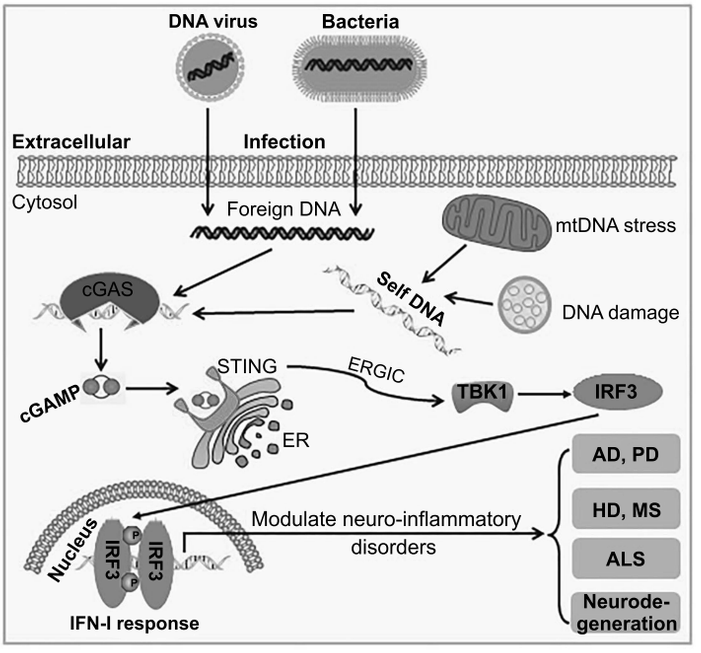

Fig. (1). Model of cGAS-STING-mediated IFN-I response in host defense and neuro-inflammatory diseases.
Abbreviations: mtDNA: mitochondrial DNA, ER: Endoplasmic reticulum, cGAS: cyclic guanosine monophosphate-adenosine monophosphate synthase, cGAMP: cyclic guanosine monophosphate-adenosine monophosphate, STING: stimulator of interferon genes, ERGIC: ER-Golgi intermediate compartment, TBK1: tank-binding kinase 1, IRF3: interferon regulatory factor 3, IFN-I: type I interferons, AD: Alzheimer's disease, PD: Parkinson's disease, HD: Huntington's disease, ALS: amyotrophic lateral sclerosis, MS: multiple sclerosis. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

with this report, a recent study indicated that a serine protease inhibitor, Bowman-Birk inhibitor (BBI), suppresses autoimmune neuroinflammation by inducing IFN-β *via* a STING-dependent pathway [31]. These findings suggest the potential therapeutic role of STING activation in MS. Noteworthily, overactivity of cGAS-STING signaling can drive STING -associated vasculopathy with onset in infancy (SAVI) and Aicardi-Goutières Syndrome (AGS) [81]; it will be important to find the optimal therapeutic levels in future treatment based on STING-directed therapies.

3.6. Other Neurodegenerative Diseases

Growing evidence implicates that aberrant STING activity and excessive IFN production are linked to interferonopathies of several autoimmune diseases, such as AGS, SAVI, systemic lupus erythematosus (SLE) and familial chilblain lupus (FCL) [82-85]. Recent studies show that spontaneous IFN response in SLE and AGS requires the cGAS/STING pathway, and the loss of DNA sensor cGAS or STING effectively suppressed the aberrant IFN-I response [82]. Gain-of-function mutations in STING also revealed the inhibitory effects of STING in SAVI and FCL. *In vitro* experiments and pioneering clinical studies suggest that attenuated STING-mediated IFN-I over-activity markedly ameliorated associated symptoms in patients [86]. Therefore, the STING-targeted interferon suppression therapeutic approach could be adapted to treat these type I interferonopathy diseases.

On the other hand, overactivation of the cGAS/STING-IFN-I pathway leading to excessive neuroinflammation in brain injury and neurodegenerative diseases has also been reported. Abdullah *et al.* found that the cGAS/STING pathway is activated after traumatic brain injury (TBI), and STING-mediated IFN-I signaling contributes to the neuroinflammatory process and detrimental effects following TBI. Moreover, in another recent study, Barrett *et al.* demonstrated that IFN-β deficiency reduces post-traumatic neuroinflammation and neurodegeneration after TBI [87, 88]. In addition, chronic neurodegeneration induces IFN-I synthesis *via* STING; the expressions of *Ifnb1* and *Irf7* were found to be significantly decreased in STING$^{-/-}$ mice [89]. Inhibition of cGAS effectively reduced the production of proinflammatory cytokines and ameliorated neurodegeneration [90]. Based on these findings, it is conceivable that cGAS/STING-dependent IFN-I response plays deleterious roles in neuroinflammation events and disease progression; inhibition of the cGAS-STING pathway may offer potential therapeutic intervention for brain injury and neurodegenerative diseases.

CONCLUSION

In recent years, several lines of evidence have indicated immunotherapy to have a protective ability against neuroinflammation and neurodegeneration in diverse neurological diseases, suggesting the prominent role of inflammatory and innate immune responses [91-93]. The discovery and characterization of the cGAS-STING pathway provide a new understanding of its innate immune-stimulatory capacity. In this review, we have summarized the fundamental roles of the cGAS-STING pathway in initiating host defense against invading pathogens, discussed its pathogenic roles in several neuro-inflammatory disorders, and presented its inhibitory roles in brain injury and neurodegenerative diseases (Fig. **1**). Taken together, cGAS/STING-mediated IFN-I signaling

produces pleiotropic cytokines that are the master regulators of antiviral immunity, controlling the pro-inflammatory cytokine secretion and contributing to the progression of multiple neuro-inflammatory diseases. Optimal pharmacological activation of the cGAS-STING pathway is undoubtedly the effective therapeutic strategy in the treatment of infections, autoimmune diseases, and neuro-inflammatory disorders. While the focus of this review was on the role of the cGAS-STING pathway in the host defense and neuro-inflammatory diseases in the future, the focus of other studies should be on the other cGAS/STING axis-mediated biological processes, such as autophagy, tumor immunogenicity, and spinal cord injury [94-96].

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
AGS	=	Aicardi-Goutières Syndrome
ALS	=	Amyotrophic Lateral Sclerosis
Aβ	=	Amyloid-beta
BBI	=	Bowman-Birk Inhibitor
CAG	=	Cytosine-adenine-guanine
cGAMP	=	Cyclic Guanosine Monophosphate-adenosine Monophosphate
cGAS	=	Cyclic Guanosine Monophosphate-adenosine Monophosphate Synthase
CNS	=	Central Nervous System
DA	=	Dopamine
DAMPs	=	Damage-associated Molecular Patterns
dsDNA	=	Double-stranded DNA
EAE	=	Experimental Autoimmune Encephalomyelitis
ER	=	Endoplasmic-reticulum
ERGIC	=	ER-Golgi Intermediate Compartment
FCL	=	Familial Chilblain Lupus
GCV	=	Ganciclovir
HD	=	Huntington's Disease
HSV-1	=	Herpes Simplex Virus 1
IFN-I	=	Type I Interferons
IRF3	=	Interferon Regulatory Factor 3
KD	=	Knockdown
LB	=	Lewy Bodies
LMN	=	Lower Motor Neuron
MAR 1	=	Monoclonal IFNAR1 Antibody
MEFs	=	Mouse Embryonic Fibroblasts
MPTP	=	1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine
MS	=	Multiple Sclerosis
NF κB	=	Nuclear Factor Kappa B
NSAIDs	=	Non-steroidal Anti-inflammatory Drugs
NTM	=	Nontuberculous Mycobacteria
PAMPs	=	Pathogen-associated Molecular Patterns
PD	=	Parkinson's Disease
PRRs	=	Pattern Recognition Receptors
SAVI	=	STING-associated Vasculopathy with On-set in Infancy
SLE	=	Systemic Lupus Erythematosus
SNpc	=	Substantia Nigra Pars Compacta
STING	=	Stimulator of Interferon Genes
TBI	=	Traumatic Brain Injury
TBK1	=	Tank-binding Kinase 1
UMN	=	Upper Motor Neuron
WNV	=	West Nile Virus

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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