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

Kai Chen1,4, Chuan Lai1, Ying Su3, Wen Dai Bao1, Liu Nan Yang1, Ping-Ping Xu2,* and Ling-Qiang Zhu1,*

1Department of Pathophysiology, Key Lab of Neurological Disorder of Education Ministry, School of Basic Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, PRC; 2Endoscopy Center, Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science and Technology, P.R China, 430015; 3Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; 4Department of Dermatology, Wuhan No. 1 Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China

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 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...
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          | Deletion of the IFN-I receptor in APP/PS1 mice preserves cognitive function | [25]  |
|                        | In-vitro cell culture         |                                                                            |       |
| Alzheimer’s disease    | In-vivo mouse model          | IFN-I signaling mediates neuro-inflammatory events in Alzheimer’s disease  | [26]  |
|                        | In-vitro cell culture         |                                                                            |       |
| 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]  |
|                        | In-vitro cell culture         |                                                                            |       |
| 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]  |
|                        | In-vitro cell culture         |                                                                            |       |
| Multiple sclerosis     | In-vitro cell culture         | BBI suppresses autoimmune neuroinflammation via STING/IFN-β axis           | [31]  |
| Amyotrophic lateral sclerosis | In-vivo mouse model          | Blocking STING prevents inflammation-related damage in ALS                | [32]  |
|                        | Patient cells                 |                                                                            |       |
| Amyotrophic lateral sclerosis | In-vivo mouse model          | Blocking STING suppresses hyperactive IFN-I responses                      | [33]  |
|                        | In-vitro cell culture         |                                                                            |       |
| Huntington’s disease   | In-vitro cell culture         | Depletion of cGAS decreases the expression of inflammatory genes          | [34]  |
| Huntington’s disease   | In-vivo mouse model          | cGAS-STING mediated inflammatory response in HD                            | [35]  |
|                        | In-vitro cell culture         |                                                                            |       |

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 neurodegenerative 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 progress 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 × IFNAR1−/− mice, found that deletion of the type-I 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-I 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 neurodegenerative 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 postmortem 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
numerous studies have shown the involvement of 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-kB-mediated pathogenic pathways [68, 69]. Indeed, the blockade of NF-kB 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
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-T−/− 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 kβ = 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.

FUNDING

The support by the National Natural Science Foundation of China (82030032, 32070960, 8196128005, 81829002, 81871108, 31721002), National Program for Support of Top-Notch Young Professionals and Academic Frontier Youth Team of Huazhong University of Science and Technology was given to Dr. Ling-Qiang Zhu; the support by the Fundamental Research Funds for the Central Universities, HUST (2019kyXJKC076) and Hubei Provincial Natural Science Foundation (2020CFB811) was given to Ying Su.

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Wu, J.; Chen, Z.J. Innate immune sensing and signaling of cytosolic nucleic acids. *Annu. Rev. Immunol.*, 2014, 32, 461-488. http://dx.doi.org/10.1146/annurev-immunol-032713-120156 PMID: 24655297

[2] Takeuchi, O.; Akira, S. Pattern recognition receptors and inflammation. *Cell*, 2010, 140(6), 805-820. http://dx.doi.org/10.1016/j.cell.2010.01.022 PMID: 20303872

[3] Kato, K.; Omura, H.; Ishitani, R.; Nureki, O. Cyclic GMP-AMP as an endogenous second messenger in innate immune signaling by cytosolic DNA. *Annu. Rev. Biochem.*, 2017, 86(1), 541-566. http://dx.doi.org/10.1146/annurev-biochem-061516-044813 PMID: 2839665

[4] Wu, J.; Sun, L.; Chen, X.; Du, F.; Shi, H.; Chen, C.; Chen, Z.J. Cyclic GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA. *Science*, 2013, 339(6121), 826-830. http://dx.doi.org/10.1126/science.1229963 PMID: 23258412

[5] Sun, L.; Wu, J.; Du, F.; Chen, X.; Chen, Z.J. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. *Science*, 2013, 339(6121), 786-791. http://dx.doi.org/10.1126/science.1232458 PMID: 23258413
TBK1-MVB12b pathway to enable paracrine cGAS-STING signaling.

Decker, T.; Paludan, S.R. Intracellular bacteria engage a STING-feron-β contributes to the clearing of non tuberculous mycobacterium bovis infection in mice. 

Weiss, S.; Goethe, R. cGAS-STING-TBK1-IRF3/7 induced inter-

Ruangkiattikul, N.; Nerlich, A.; Abdissa, K.; Lienenklaus, S.; Su-

Li, Q.; Liu, C.; Yue, R.; El-Ashram, S.; Wang, J.; He, X.; Zhao, D.; 

Kawai, T.; Akira, S. Innate immune recognition of viral infection. 

Wu, Y.T.; Grishin, N.V. Phosphorylation of innate immune adaptor proteins MAVS, STING, and TRIF induces IRF3 activation. 

Barbalat, R.; Ewald, S.E.; Mouche ss, M.L.; Barton, G.M. Nucleic acid recognition by the innate immune system. 

Immunity, 2008, 29(4), 538-550. 

Sun, W.; Li, Y.; Chen, L.; Chen, H.; You, F.; Zhou, X.; Zhou, Y.; Zhai, Z.; Chen, D.; Jiang, Z. ERIS, an endoplasmic reticulum IFN stimulator, activates innate immune signaling through dimerization. 

Proc. Natl. Acad. Sci. USA, 2009, 106(21), 8653-8658. 

Chen, Q.; Sun, L.; Chen, Z.J. Regulation and function of the cGAS-STING pathway of cytosolic DNA sensing. 

Nat. Immunol., 2016, 17(10), 1142-1149. 

http://dx.doi.org/10.1038/natureni.3558 PMID: 27648547 

de Weerd, N.A.; Samarajiva, S.A.; Hertzog, P.J.; Type, I Type I interferon receptors: biochemistry and biological functions. J. Biol. Chem., 2007, 282(28), 20503-20507. 

http://dx.doi.org/10.1074/jbc.R70006200 PMID: 17502368 

Nandakumar, R.; Tschischarov, M.; Meissner, F.; Prabakaran, T.; Kriissanaprati, A.; Farahani, E.; Zhang, B.C.; Assil, S.; Martin, A.; Bertrams, W.; Holm, C.K.; Ablasser, A.; Krause, T.; Thomsen, M.K.; Schmeck, B.; Howard, K.A.; Henry, T.; Goethel, K.V.; Decke, T.; Paladan, S.R. Intracellular bacteria engage a STING-TBK1-MVB12b pathway to enable paracrine cGAS-STING signaling. 

Nat. Microbiol., 2019, 4(4), 701-713. 

http://dx.doi.org/10.1038/s41556-019-0367-2 PMID: 30804548 

Li, Q.; Liu, C.; Yue, R.; El-Ashram, S.; Wang, J.; He, X.; Zhao, D.; Zhou, X.; Xu, L. cGAS-STING/TBK1/IRF3 signaling pathway activates BMDCs maturation following mycobacterium bovis infec-

http://dx.doi.org/10.1074/jbc.R17000620 PMID: 17502368 

http://dx.doi.org/10.1038/s41556-019-0367-2 PMID: 30804548 

Ruangkiattikul, N.; Nerlich, A.; Abdissa, K.; Lienenklaus, S.; Su-

Wan
di, A.; Janze, N.; Laarmann, K.; Spanier, J.; Kalincke, U.; Weiss, S.; Goethe, R. cGAS-STING/TBK1-IRF3/7 induced inter-

feron-β contributes to the clearing of non tuberculous mycobacteri-

al infection in mice. 

Virulence, 2017, 8(7), 1303-1315. 

http://dx.doi.org/10.1080/21505594.2017.1321911 PMID: 28422568 

McGuekin Wuertz, K.; Treuting, P.M.; Hemmann, E.A.; Esse-

Nobis, K.; Snyder, A.G.; Graham, J.B.; Daniels, B.P.; Wilkins, C.; Snyder, J.M.; Voss, K.M.; Oberst, A.; Lund, J.; Gale, M., Jr STING is required for host defense against neuropathological West Nile vi-

rus infection. PLoS Pathog., 2019, 15(6), e1007899. 

http://dx.doi.org/10.1371/journal.ppat.1007899 PMID: 31456767 

Mathur, V.; Burali, R.; Vest, R.T.; Bonanno, L.N.; Lehali
er, B.; Zardeneta, M.E.; Mistry, K.N.; Do, D.; Marsh, S.E.; Abud, E.M.; Blurton-Jones, M.; Li, L.; Lashuel, H.A.; Wyss-Coray, T. Activation of the STING-Dependent Type I interferon response reduces microglial reactivity and neuroinflammation. 

Neuron, 2017, 96(6), 1290-1302.e6. 

http://dx.doi.org/10.1016/j.neuron.2017.11.032 PMID: 29268096 

Jia, M.; Qin, D.; Zhao, C.; Chai, L.; Yu, Z.; Wang, W.; Tong, L.; 

Lv, L.; Wang, Y.; Rehwinkel, J.; Yu, J.; Zhao, W. Redox homeo-

stasis maintained by GPX4 facilitates STING activation. 

Nat. Immunol., 2020, 21(7), 727-735. 

http://dx.doi.org/10.1038/s41590-020-0699-0 PMID: 32541831 

Minter, M.R.; Moore, Z.; Zhang, M.; Brody, K.M.; Jones, N.C.; Shultz, S.R.; Taylor, J.M.; Crack, P.J. Deletion of the type-I interferon receptor in APPSVSE/PS1AE9 mice preserves cognitive function and alters glial phenotype. Acta Neuropathol. Commun., 2016, 4(1), 72-72. 

http://dx.doi.org/10.1186/s40478-016-0341-4 PMID: 27400725 

Taylor, J.M.; Minter, M.R.; Newman, A.G.; Zhang, M.; Adlard, P.A.; Crack, P.J. Type-I interferon signaling mediates neuro-

inflammatory events in models of Alzheimer’s disease. 

Neurobiol. Aging, 2014, 35(5), 1012-1023. 

http://dx.doi.org/10.1016/j.neurobiolaging.2013.10.089 PMID: 24262201 

Mesquita, S.D.; Ferreira, A.C.; Gao, F.; Coppola, G.; Geschwind, D.H.; Sousa, J.C.; Correia-Neves, M.; Sousa, N.; Palha, J.A.; Marques, F. The chondriol plexus transcriptome reveals changes in type I and II interferon responses in a mouse model of Alzheimer’s disease. 

Brain Behav. Immun., 2015, 49, 280-292. 

http://dx.doi.org/10.1016/j.bbi.2015.06.008 PMID: 26092102 

Main, B.S.; Zhang, M.; Brody, K.M.; Aytos, S.; Frugier, T.; Steer, D.; Finkelstein, D.; Crack, P.J.; Taylor, J.M. Type-I interferons contribute to the neuroinflammatory response and disease progression of the MPTP mouse model of Parkinson’s disease. 

Glia, 2016, 64(9), 1590-1604. 

http://dx.doi.org/10.1002/glia.23028 PMID: 27404846 

Sliter, D.A.; Martinez, J.; Hao, L.; Chen, X.; Sun, N.; Fischer, T.D.; Burman, J.L.; Li, Y.; Zhang, Z.; Narendran, D.P.; Cai, H.; Bouche, M.; Kleijer, W.J.; Parkin and PINK1 mitigate STING-induced inflammation. 

Nature, 2018, 561(7722), 258-262. 

http://dx.doi.org/10.1038/s41586-018-0448-9 PMID: 30153585 

Helbi, S.; Ravanbakhsh, B.; Karimi, M.; Kooti, W.; Jivad, N. Aligned Expression of IFI16 and STING Genes in RRMS Patients’ Blood. 

Endocr. Metab. Immune Disord. Drug Targets, 2019, 19, 1-9. 

Casella, G.; Rasouli, J.; Mason, K.; Boehm, A.; Kumar, G.; Hwang, D.; Thomé, R.; Ishikawa, L.; Zhang, G-X.; Ciric, B.; Ros-

Romi, A. Serine protease inhibitor suppresses autoimmune neu-

roinflammation by activating the STING/IFN-β axis in macrophag-

es. Cell. Mol. Immunol., 2020, 17(12), 1278-1280. 

http://dx.doi.org/10.1016/j.cmi.2020-04-040-z PMID: 32203194 

Yu, C.H.; Davidson, S.; Harapas, C.R., Hilton, J.B.; Mldziosnki, M.J.; Laohamonthonkul, P.; Louis, C.; Low, R.R.J.; Moeking, J.; De Nardo, D.; Balka, K.R.; Calleja, D.J.; Moecking, J.; McCauley, M.E.; O’Rourke, J.G.; Yáñez, A.; Markman, J.L.; Ho, P.; Wang, X.; Chen, S.; Lall, D.; Jin, M.; Muhammad, A.K.M.G.; Bell, S.; Landeros, J.; Valencia, V.; Harms, M.; Arditii, M.; Jeffer-

ies, C.; Baloh, R.H. COIF2 in myeloid cells suppresses STING-

induced inflammation. Nature, 2020, 585(7823), 96-101. 

http://dx.doi.org/10.1038/s41586-020-2625-x PMID: 32814898
cGAS-STING-mediated IFN-I Response in Host Defense

Current Neuropharmacology, 2022, Vol. 20, No. 2 369

interferon response in vitro. J. Neuroinflammation, 2015, 12(1), 71-71.

http://dx.doi.org/10.1186/s12974-015-0263-2 PMID: 25879763

Postuma, R.B.; Berg, D.; Stern, M.; Poewe, W.; Olanow, C.W.; Oertel, W.; Obeso, J.; Marek, K.; Litvan, I.; Lang, A.E.; Halliday, G.; Goetz, C.G.; Gasser, T.; Dubois, B.; Chan, P.; Bloem, B.R.; Adler, C.H.; Deuschl, G. MDS clinical diagnostic criteria for Parkinson’s disease. Mov. Disord., 2015, 30(12), 1591-1601. http://dx.doi.org/10.1002/mds.26424 PMID: 26474316

Yao, L.; Ye, Y.; Mao, H.; Lu, F.; He, X.; Lu; G.; Zhang, S. MicroRNA-124 regulates the expression of MEKK3 in the inflammatory pathogenesis of Parkinson’s disease. J. Neuroinflammation, 2018, 15(1), 13-12.

http://dx.doi.org/10.1186/s12974-018-1053-4 PMID: 29329581

Sun, Q.; Wang, S.; Chen, J.; Cai, H.; Huang, W.; Zhang, Y.; Wang, L.; Xing. MicroRNA-190 alleviates neuronal damage and inhibits its neuroinflammation via Nlrp3 in MPTP-induced Parkinson’s disease mouse model. J. Cell. Physiol., 2019, 234(12), 2379-2383. http://dx.doi.org/10.1002/jcp.28907 PMID: 31232742

Sampson, T.R.; Debelius, J.W.; Thron, T.; Janssen, S.; Shastri, G.G.; Ilhan, Z.E.; Challis, C.; Schetter, C.E.; Rocha, S.; Gradinaru, V.; Chesselet, M.F.; Keshavarzian, A.; Shannon, K.M.; Kramalnik-Brown, R.; Wittung-Stafshede, P.; Knight, R.; Mazmanian, S.K. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson’s Disease. Cell, 2016, 167(6), 1469-1480.e12.

http://dx.doi.org/10.1016/j.cell.2016.11.018 PMID: 27912057

Gelders, G.; Baekelandt, V.; Der Perren, A.V. Linking neuroinflammation and neurodegeneration in Parkinson’s Disease. Clin. Develop. Immunol. 2018, 2018, 4784268. http://dx.doi.org/10.1155/2018/4784268

Nicoletti, A.; Fagone, P.; Donzuso, G.; Mangano, K.; Dibilio, I.; Caponnetto, S.; Bendtzen, K.; Zappia, M.; Nicoletti, F. Parkinson’s disease is associated with increased serum levels of macrophage migration inhibition factor. Cytochrome. 2011, 55(2), 165-167.

http://dx.doi.org/10.1159/2011.0022 PMID: 21558014

Watson, M.B.; Richter, F.; Lee, S.K.; Gabby, L.; Wu, J.; Masliah, E.; Effros, R.B.; Cheselet, M.F. Regionally-specific microglial activation in young mice over-expressing human wildtype alpha-synuclein. Exp. Neuro., 2012, 237(2), 318-334. http://dx.doi.org/10.1016/j.expneurol.2012.06.025 PMID: 23068277

Gao, D.; Li, T.; Li, X.D.; Chen, X.; Li, Q.Z.; Wight-Carter, M.; Chen, Z.J. Activation of cyclic GMP-AMP synthase by self-DNA causes autoimmune diseases. Proc. Natl. Acad. Sci. USA., 2015, 112(42), E5699-E5705. http://dx.doi.org/10.1073/pnas.1516465112 PMID: 26371324

Walker, F.O. Huntington’s disease. Lancet, 2007, 369(9557), 218-228. http://dx.doi.org/10.1016/S0140-6736(07)60111-1 PMID: 17240289

Bates, G.P.; Dorsey, R.; Gusella, J.F.; Hayden, M.R.; Kay, C.; Leavitt, B.R.; Nance, M.; Ross, C.A.; Seabill, R.T.; Wetzol, R.; Wild, E.J.; Tabrizi, S.J. Huntington disease. Nat. Rev. Dis. Primers. 2015, 1, 15005. http://dx.doi.org/10.1038/nrd.2015.5 PMID: 27188817

Denis, H.L.; Lauruol, F.; Cicchetti, F. Are immunotherapies for Huntington’s disease a realistic option? Mol. Psychiatry, 2019, 24(3), 364-377. http://dx.doi.org/10.1038/s41380-018-0021-9 PMID: 29487401

Träger, U.; Andre, R.; Lahrin, N.; Magnusson-Lind, A.; Weiss, A.; Grueninger, S.; McKinnon, C.; Srinathisingh, J.; Kahan, S.; Pilsier, E.L.; Moser, R.; Hummerich, H.; Antoniou, M.; Bates, G.P.; Luthi-Carter, R.; Lowell, M.W.; Björkqvist, M.; Ostrow, G.R.; Aronin, N.; Tabrizi, S.J. HTT lowering reverses Huntington’s disease immune dysfunction caused by NFXB pathway dysregulation. Brain, 2014, 137(Pt 3), 819-833. http://dx.doi.org/10.1093/brain/awt355 PMID: 24459107

Björkqvist, M.; Wild, E.J.; Thiele, J.; Silverstrom, A.; Andre, R.; Lahrin, N.; Raison, E.; Lee, R.V.; Meng, C.L.; Soulet, D.; Magnusson, A.; Woodman, B.; Landles, C.; Pouladi, M.A.; Hayden, M.R.; Khalili-Shirazi, A.; Lowell, M.W.; Brundin, P.; Bates, G.P.; Leavitt, B.R.; Möller, T.; Tabrizi, S.J. A novel pathogenic pathway
microglial phagocytosis of degenerating axons. J. Neurosci., 2012, 32(22), 7745-7757.
http://dx.doi.org/10.1523/JNEUROSCI.0203-12.2012 PMID: 22649252

Khorooshi, R.; Owens, T. Injury-induced type I IFN signaling regulates inflammatory responses in the central nervous system. J. Immunol., 2010, 185(2), 1258-1264.
http://dx.doi.org/10.4049/jimmunol.0901753 PMID: 20562259

Galligan, C.L.; Pennell, L.M.; Murooka, T.T.; Baig, E.; Majchrzak-Kita, B.; Rahbar, R.; Fish, E.N. Interferon-β is a key regulator of proinflammatory events in experimental autoimmune encephalomyelitis. Mult. Scler., 2010, 16(12), 1458-1473.
http://dx.doi.org/10.1177/1352458510381259 PMID: 20935030

Teige, I.; Treschow, A.; Teige, A.; Mattisson, R.; Navikas, V.; Leanderson, T.; Holmdahl, R.; Issazadeh-Navikas, S. IFN-beta gene deletion leads to augmented and chronic demyelinating experimental autoimmune encephalomyelitis. J. Immunol., 2003, 170(9), 4776-4784.
http://dx.doi.org/10.4049/jimmunol.170.9.4776 PMID: 12707359

Salem, M.; Mony, J.T.; Lobner, M.; Khoroooshi, R.; Owens, T. Interferon regulatory factor-7 modulates experimental autoimmune encephalomyelitis in mice. J. Neuroinflammation, 2011, 8(1), 181-181.
http://dx.doi.org/10.1186/1742-4040-8-181 PMID: 21968084

Wengerchuk, D.M.; Carter, J.L. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. Mayo Clin. Proc., 2014, 89(2), 225-240.
http://dx.doi.org/10.1016/j.mayocp.2013.11.002 PMID: 24841535

Rodero, M.P.; Crow, J.Y. Type I interferon-mediated monogenic autoinflammation: The type I interferonopathies, a conceptual overview. J. Exp. Med., 2016, 123(12), 2527-2538.
http://dx.doi.org/10.1084/jem.20161596 PMID: 27821552

Li, Y.; Wilson, H.L.; Kiss-Toth, E. Regulating STING in health and disease. J. Inflamm. (Lond.), 2017, 14(1), 11-11.
http://dx.doi.org/10.1186/s12950-017-0159-2 PMID: 2859706

Melki, I.; Rose, Y.; Uggenti, C.; Van Execk, L.; Frénod, M.L.; Kitabayashi, N.; Rice, G.J.; Jenkinson, E.M.; Boulai, A.; Jeremiah, N.;Gattorno, M.; Volpi, S.; Sacco, O.; Terheggen-Lagro, S.W.J.; Tiddens, H.A.W.M.; Meys, I.; Morren, M.A.; De Haes, P.; Wouters, C.; Legius, E.; Corveleyn, A.; Rieux-Laucat, F.; Bodemer, C.; Callebaut, I.; Rodero, M.P.; Crow, J.Y. Disease-associated mutations identify a novel region in human STING necessary for the control of type I interferon signaling. J. Allergy Clin. Immunol., 2017, 140(2), 543-552.e5.
http://dx.doi.org/10.1016/j.jaci.2016.10.031 PMID: 28087229

Bialas, A.R.; Presumey, J.; Das, A.; van der Poel, C.E.; Lapach, P.H.; Mesin, L.; Vietor, G.; Tsakos, G.C.; Mawrin, C.; Herbst, R.; Carroll, M.C. Microglia-dependent synapse loss in type I interferon-mediated lupus. Nature, 2017, 546(7659), 539-543.
http://dx.doi.org/10.1038/nature22821 PMID: 28614301

Crow, J.Y.; Manel, N. Aicardi-Goutières syndrome and the type I interferonopathies. Nat. Rev. Immunol., 2015, 15(7), 429-440.
http://dx.doi.org/10.1038/nri3850 PMID: 26052908

Liu, Y.; Jesus, A.A.; Marrero, B.; Yang, D.; Ramsey, S.E.; Sanchez, G.A.M.; Tenbrock, K.; Wittkowski, H.; Jones, O.Y.; Kuhle, A.G.; O'D.; Ritzel, R.M.; Meadows, V.A.; Vogel, S.N.; Faden, A.I.; Stoi...
ca, B.A.; Loane, D.J. Interferon-β plays a detrimental role in experimental traumatic brain injury by enhancing neuroinflammation that drives chronic neurodegeneration. J. Neurosci., 2020, 40(11), 2357-2370.
http://dx.doi.org/10.1523/JNEUROSCI.2516-19.2020 PMID: 32029532

[89] Nazmi, A.; Field, R.H.; Griffin, E.W.; Haugh, O.; Hennessy, E.; Cox, D.; Reis, R.; Tortorelli, L.; Murray, C.L.; Lopez-Rodriguez, A.B.; Jin, L.; Lavelle, E.C.; Dunne, A.; Cunningham, A. Chronic neurodegeneration induces type I interferon synthesis via STING, shaping microglial phenotype and accelerating disease progression. Glia, 2019, 67(7), 1254-1276.
http://dx.doi.org/10.1002/glia.23592 PMID: 30680794

[90] Li, Q.; Cao, Y.; Dang, C.; Han, B.; Han, R.; Ma, H.; Hao, J.; Wang, L. Inhibition of double-strand DNA-sensing cGAS ameliorates brain injury after ischemic stroke. EMBO Mol. Med., 2020, 12(4), e11002.
http://dx.doi.org/10.15252/emmm.201911002 PMID: 32329625

[91] Ryu, J.K.; Rafalski, V.A.; Meyer-Franke, A.; Adams, R.A.; Podda, S.B.; Rios Coronado, P.E.; Pedersen, L.O.; Menon, V.; Baeten, K.M.; Sikorski, S.L.; Bedard, C.; Hanspers, K.; Bardehle, S.; Mendiola, A.S.; Davalos, D.; Machado, M.R.; Chan, J.P.; Plastira, I.; Petersen, M.A.; Pfaff, S.J.; Ang, K.K.; Hallenbeck, K.K.; Syne, C.; Hakozaki, H.; Ellisman, M.H.; Swanson, R.A.; Zamvil, S.S.; Arkin, M.R.; Zorn, S.H.; Pico, A.R.; Mucke, L.; Freedman, S.B.; Stavenhagen, J.B.; Nelson, R.B.; Akassoglou, K. Fibrin-targeting immunotherapy protects against neuroinflammation and neurodegeneration. Nat. Immunol., 2018, 19(11), 1212-1223.
http://dx.doi.org/10.1038/s41590-018-0232-x PMID: 30323343

[92] Rivest, S. Regulation of innate immune responses in the brain. Nat. Rev. Immunol., 2009, 9(6), 429-439.
http://dx.doi.org/10.1038/nri2565 PMID: 19461673

[93] Ransohoff, R.M.; Brown, M.A. Innate immunity in the central nervous system. J. Clin. Invest., 2012, 122(4), 1164-1171.
http://dx.doi.org/10.1172/JCI1758644 PMID: 22466658

[94] Liu, D.; Wu, H.; Wang, C.; Li, Y.; Tian, H.; Siraj, S.; Sehgal, S.A.; Wang, X.; Wang, J.; Shang, Y.; Jiang, Z.; Liu, L.; Chen, Q. STING directly activates autophagy to tune the innate immune response. Cell Death Differ., 2019, 26(9), 1735-1749.
http://dx.doi.org/10.1038/s41418-018-0251-z PMID: 30568238

[95] Wang, Z.; Chen, J.; Hu, J.; Zhang, H.; Xu, F.; He, W.; Wang, X.; Li, M.; Lu, W.; Zeng, G.; Zhou, P.; Huang, P.; Chen, S.; Li, W.; Xia, L.P.; Xia, X. cGAS/STING axis mediates a topoisomerase II inhibitor-induced tumor immunogenicity. J. Clin. Invest., 2019, 129(11), 4850-4862.
http://dx.doi.org/10.1172/JCI127471 PMID: 31408442

[96] Wang, Y.Y.; Shen, D.; Zhao, L.J.; Zeng, N.; Hu, T.H. Sting is a critical regulator of spinal cord injury by regulating microglial inflammation via interacting with TBK1 in mice. Biochem. Biophys. Res. Commun., 2019, 517(4), 741-748.
http://dx.doi.org/10.1016/j.bbrc.2019.07.125 PMID: 31400857