Cell Communication and Signaling

REVIEW

Open Access

cGAS-STING, inflammasomes and pyroptosis: an overview of crosstalk mechanism of activation and regulation

Jingwen Liu[1,2†], Jing Zhou[3†], Yuling Luan[4†], Xiaoying Li[5], Xiangrui Meng[1], Wenhao Liao[1], Jianyuan Tang[1,2*] and Zheilei Wang[1,2*]

Abstract

Background Intracellular DNA-sensing pathway cGAS-STING, inflammasomes and pyroptosis act as critical natural immune signaling axes for microbial infection, chronic inflammation, cancer progression and organ degeneration, but the mechanism and regulation of the crosstalk network remain unclear.

Main body of the abstract Cellular stress disrupts mitochondrial homeostasis, facilitates the opening of mitochondrial permeability transition pore and the leakage of mitochondrial DNA to cell membrane, triggers inflammatory responses by activating cGAS-STING signaling, and subsequently induces inflammasomes activation and the onset of pyroptosis. Meanwhile, the inflammasome-associated protein caspase-1, Gasdermin D, the CARD domain of ASC and the potassium channel are involved in regulating cGAS-STING pathway. Importantly, this crosstalk network has a cascade amplification effect that exacerbates the immuno-inflammatory response, worsening the pathological process of inflammatory and autoimmune diseases. Given the importance of this crosstalk network of cGAS-STING, inflammasomes and pyroptosis in the regulation of innate immunity, it is emerging as a new avenue to explore the mechanisms of multiple disease pathogenesis. Therefore, efforts to define strategies to selectively modulate cGAS-STING, inflammasomes and pyroptosis in different disease settings have been or are ongoing. In this review, we will describe how this mechanistic understanding is driving possible therapeutics targeting this crosstalk network, focusing on the interacting or regulatory proteins, pathways, and a regulatory mitochondrial hub between cGAS-STING, inflammasomes, and pyroptosis.

Short conclusion This review aims to provide insight into the critical roles and regulatory mechanisms of the crosstalk network of cGAS-STING, inflammasomes and pyroptosis, and to highlight some promising directions for future research and intervention.

Keywords cGAS-STING, Inflammasome, Pyroptosis, Inflammation, Crosstalk network, Diseases

†Jingwen Liu, Jing Zhou and Yuling Luan are co-first author.

*Correspondence:
Jianyuan Tang
tangjy@cdutcm.edu.cn
Zheilei Wang
wangzl1993@outlook.com
Full list of author information is available at the end of the article

Background

Stimulator of interferon genes (STING) is a cell membrane DNA sensor widely distributed in the endoplasmic reticulum (ER) of mammalian immune cells, which is a vital mediator to regulate innate immune responses. Activation of STING confers host immunity and is key to the clearance of a variety of pathogens, including viruses and bacteria [1–3]. As a DNA recognition receptor, cyclic GMP-AMP synthase (cGAS) recognizes and binds double-stranded DNA (dsDNA) of both foreign and self-origin without sequence differences. cGAS enzymatically converts adenosine triphosphate (ATP) and guanosine triphosphate (GTP) to 2'-3' cyclic GMP-AMP (cGAMP). cGAMP acts as a second messenger to potently agonize the ER membrane protein STING. STING subsequently recruits and activates TANK-binding kinase 1 (TBK1) to initiate downstream signaling, which in turn promotes the phosphorylation of interferon (IFN) regulatory factor 3 (IRF3), while STING promotes nuclear factor-kappa B (NF-κB) phosphorylation by activating IκB kinase (IKK). IRF3 is then dimerized and translocated to the nucleus with NF-κB to induce *type I* IFN and other cytokines [4–7]. We note that major drug discovery efforts are currently underway to explore and identify agonists of the cGAS-STING pathway as vaccine adjuvants or as anticancer immunostimulants [8–11]. In immunocompetent mice with established syngeneic colon tumors, intravenous administration of a synthetic, non-nucleotide-based diABZI STING agonist exhibits potent anti-tumor activity [12]. Vaccines adjuvated with STING agonists have been shown to elicit potent immune responses against infection and cancer [13]. The natural STING agonist, cGAMP, is a potent adjuvant that improves the immunogenicity of nanoparticulate Influenza A vaccines by enhancing humoral, cellular and mucosal immune responses in mice [14, 15]. In addition, excessive STING activation has been identified as contributing to the progression of various inflammatory diseases [16–19].

Inflammasomes, such as NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) and absent in melanoma 2 (AIM2), initiate the release of pro-inflammatory cytokines upon receipt of danger signals to activate the innate immune response and are essential for the clearance of pathogens or damaged cells. NLRP3 is an intracellular sensor that recognizes a wide variety of microbial motifs, endogenous danger signals and environmental irritants, triggering the formation and activation of the NLRP3 inflammasome. A two-step process of priming and activation is required for NLRP3 inflammasome [20]. In the priming stage, NF-κB is first activated by recognition receptors such as Toll-like receptors (TLRs) that recognize pathogen-associated molecular patterns (PAMPs) or danger signaling molecular patterns (DAMPs), followed by upregulation of NLRP3 and pro-IL-1β [21]. During the activation stage, the inflammasome complex (NLRP3-ASC-caspase-1) is assembled and activated by various inducers, such as viral, bacterial, various interventions [22–24]. Once activated, caspase-1 subsequently functions to result in pyroptosis and cleavage of the proinflammatory cytokines pro-IL-1β and pro-IL-18 into their bioactive forms IL-1β and IL-18, to amplify the inflammatory response [25]. Upon the activation of AIM2 inflammasome, the effector protein caspase-1 is recruited to the complex and cleaves gasdermin D (GSDMD) to release the GSDMD-N fragment, inducing pyroptosis and the release of cellular contents [26]. Pyroptosis is a type of pro-inflammatory programmed cell death that is marked by cell dilation, formation of plasma membrane pores, rapid cell degradation, and the release of inflammatory cytokines [27]. Pyroptosis contributes to the protection of the body from infections such as bacteria, but excessive pyroptosis can lead to chronic inflammation and immune disorders [28–31].

The last decade has witnessed a dramatic appreciation of inflammasomes, pyroptosis and cGAS-STING as critical innate immune components that orchestrate host immune homeostasis. Although inflammasomes, pyroptosis and cGAS-STING are relatively independent innate immune signaling pathways, there is an intracellular signaling network between cGAS-STING, inflammasomes and pyroptosis. In this review, we focus on recent findings regarding the impact of this crosstalk network as a primary driver of inflammatory diseases. We briefly highlight the current state of understanding of signaling through the cGAS-STING, inflammasomes, and pyroptosis pathways, summarize the molecular mechanisms in different pathophysiological contexts, and analyze their involvement in preclinical disease models. On this basis, the key molecular events underlying the crosstalk between cGAS-STING, inflammasomes and pyroptosis were elucidated. In addition, in view of the important role of this crosstalk network in the innate immune response, we also concentrate on the emergence of pharmacological approaches that target the crosstalk network and demonstrate their potential for clinical application. A better understanding of the crosstalk network of cGAS-STING, inflammasomes and pyroptosis will guide the development of therapeutic strategies to combat infectious and inflammatory diseases.

Inflammasomes and pyroptosis regulate cGAS-STING

AIM2 inflammasome regulates cGAS-STING

The STING-*type I* IFN and AIM2 inflammasome activated by DNA ligands may be crucial to elucidate (Fig. 1). In dendritic cells (DCs) and macrophages deficient in

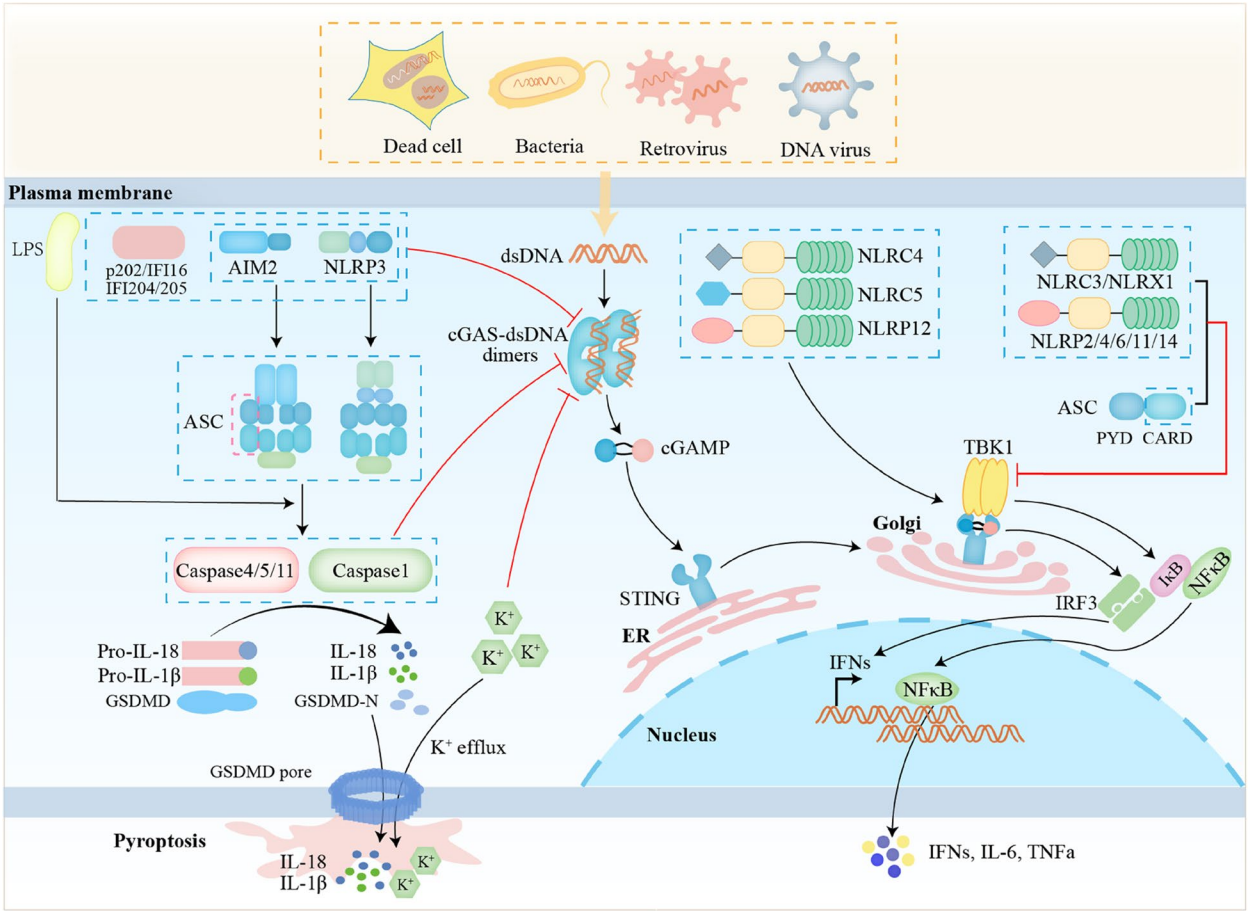

Fig. 1 Inflammasomes and pyroptosis regulate cGAS-STING. AIM2 and NLRP3 proteins, AIM2-like receptors, caspase-1, GSDMD, the CARD domain of ASC, potassium channel, and Nod-like receptors are involved in regulating cGAS-STING pathway

AIM2, ASC, or caspase-1, cGAMP production, STING aggregation, and TBK1 and IRF3 phosphorylation were significantly enhanced upon cytosolic DNA exposure [32], demonstrating that the inhibition of the STING pathway by the AIM2 impacts upstream STING, thus reducing the entire STING pathway activation cascade. Similarly, AIM2 deficiency led to large aggregates of macrophages ($CXCR3^{+}CD206^{+}$) activate the STING-TBK1-IRF3/NF-κB pathway in response to dsDNA, resulting in pro-inflammatory cytokines maturation and secretion, including C-X-C motif chemokine 10 (CXCL10), TNFα, and IFN-β [33]. *Mycobacterial* infection of $Aim2^{-/-}$ mice induced the production of large amounts of IFN-β and depressed IFN-γ secretion through suppressing the interaction between STING and downstream TBK1 in macrophages and DCs [34], resulting in higher infection loads and more severe pathology. Thus, these findings suggest that the AIM2 negatively regulates the cGAS-STING-driven production of *type I* IFN upon stimulation with various DNA forms.

AIM2-like receptors (ALRs) regulate cGAS-STING

ALRs are essential for the *type I* IFN response to endogenous host DNA and determine the course of infections, inflammatory diseases, aging, and cancer [35–37]. Studies have shown that activation of ALRs is associated with host protection following recognition of bacterial DNA, a process that can occur via direct DNA sensing or indirect sensing of pathogen-associated intracellular alterations [36]. Some members of the ALRs gene family were involved in the cGAS-STING pathway (Fig. 1), e.g., IFI204, IFI205 and the human homologue of IFI204, IFI16 [38–40]. Most known ALRs are excellent candidates for innate immune DNA receptors because they have both a pyrin domain, which mediates protein-protein interactions, and a HIN domain, which directly bind to DNA [41]. The pyrin-only protein PYR-A and the HIN-only protein IFI202b are exceptions among the murine ALRs that potently activate STING [38]. The p202 protein encoded by the IFI202 gene, IFI204 and IFI205 have been shown to be negative regulators of

AIM2 inflammasome, which cooperated to sense cytosolic dsDNA to produce a strong *type I* IFN response through activation of cGAS-STING [42–44]. IFI202b expression levels likely contribute to mouse strain-specific susceptibility to Theiler's murine encephalomyelitis virus (TMEV)-induced central nervous system (CNS) lesions [45]. In accordance with this, TMEV-infected IFN-$\beta^{-/-}$ C57BL/6 mice show an impaired virus elimination capacity and 70% of these mice develop mild demyelination [45]. The mouse ALR IFI205 senses self-DNA derived from retrotransposons in the cytoplasm of macrophages and activates the *type I* IFN signaling pathway via STING [42]. Notably, the p200 family proteins, represented by IFI204, which is well known as an ALR and murine ortholog of IFI16 [46, 47], were markedly induced in bone marrow-derived dendritic cells (BMDCs) after infection by mouse hepatitis coronavirus (MHV), which belongs to the same genus betacoronavirus as SARS-CoV and MERS-CoV to mimic the acute RNA virus infection [48]. Moreover, the consistent phenomena in HSV-1-infected A549 cells with IFI16$^{-/-}$, indicating that IFI204 might facilitate cGAS-STING DNA sensing pathway that leads to IRF3 activation during the infection of HSV-1 [48]. Similarly, knockdown of IFI204 by small interfering RNA significantly inhibited IFN-β release in response to bacterial infections such as *Francisella novicida* [44], *Mycobacterium bovis* [49], *Staphylococcus aureus* [50], demonstrating IFI204 is essential for host defense against intracellular and extracellular bacterial infection.

IFI16, a sequence-independent nuclear innate sensor ALR, was also proposed to stimulate other cellular pathways upon its binding to viral DNA [40]. Several reports assert that DNA of *herpesviruses Kaposi's sarcoma-associated herpesvirus* (KSHV), *Epstein-Barr virus* (EBV), and *herpes simplex virus 1* (HSV-1) during infection assembles an IFI16-containing oligomeric structure, leading to the production of active caspase-1 and IL-1β [51, 52]. Furthermore, during HSV-1 infection, IFI16 recognizes HIV-1 proviral DNA in nuclei of infected human foreskin fibroblasts (HEFs), inducing IFN-β production via the cytoplasmic STING-TBK1-IRF3 pathway [51, 53]. Besides, IFI16 was also reported to sense *Listeria monocytogenes* DNA in human macrophages, inducing IFN-β expression in a manner dependent on cGAS-STING [54].

NLRP3 inflammasome regulates cGAS-STING

NLRP3 inflammasome is composed of the cytoplasmic sensor NLRP3, the adaptor ASC and the effector caspase-1. Elevated *p*-TBK1 and *p*-IRF3 in colonic tissues and enhanced IFN-β levels after NLRP3 deficiency were observed in the mice subjected to whole abdomen radiation by timed exposure to X-ray at a cumulative dose [55], suggesting that NLRP3 deficiency led to an increase in cGAS-STING-mediated IFN-β production by radiation. NLRP3 deficiency increased the production of *type I* IFN and enhanced the resistance of the host to Zika virus in vitro and in vivo [56], which unraveled a novel antagonistic mechanism by which Zika suppresses the host immune response by manipulating the interplay between inflammasome and *type I* IFN signaling, which might guide the rational design of therapeutics in the future.

Caspases regulate cGAS-STING

Increased IFN production in response to DNA viral infection, but not RNA viral attack, was detected in the inflammatory response of Casp-1$^{-/-}$ macrophages [57]. Caspase-1 interacted with cGAS during canonical and non-canonical inflammasome activation, cleaved cGAS and inhibited STING-mediated IFN production [57]. Upon inflammasome activation, caspase-1 binded directly to cGAS via its p20 domain and cleaved human cGAS at the D140/157 site, leading to a reduction in cGAMP production and cytokine expression. Also, caspase-4 and caspase-5 in humans and caspase-11 in mice cleaved cGAS in lipopolysaccharide (LPS)-induced activation of non-canonical inflammasome [57]. Consistently, induction of cGAS cleavage during Zika virus infection by caspase-1 inhibited phosphorylation of TBK1 and IRF3 and reduced *type I* IFN production, thereby evading the antiviral response [56]. In conclusion, canonical and non-canonical inflammasome activation induce the production of active caspase-1, which interacts with cGAS and in turn inhibits cGAS-STING-mediated *type I* IFN production (Fig. 1).

GSDMD regulates cGAS-STING

The pore forming activity of GSDMD is located in gasdermin-N domain, while the gasdermin-C domain inhibits its pore forming activity. The release of gasdermin-N domain migrated to the cell membrane, formed pores with an inner diameter of 10–15 nm, thereby promoting pyroptosis [58–61]. Mice deficient in GSDMD exhibited an enhanced IFN-β response to *Francisella novicida* infection, and GSDMD negatively regulated the IFN-β response in a manner independent of pyroptosis and IL-1β [62]. GSDMD activated by AIM2 inflammasome depleted intracellular K^+ through the membrane pores, which is sufficient and essential for the inhibition of the cGAS-dependent IFN-β response, and thereby inhibited the cGAS-driven *type I* IFN response to macrophage DNA and *F. novicida* infection [62]. In summary, the GSDMD-K^+ efflux axis targets cGAS to reduce the synthesis of cGAMP, thereby inhibiting STING signaling and reducing IFN-β production (Fig. 1).

The CARD domain of ASC regulates cGAS-STING

The ligand protein ASC consists of two domains, a PYD domain at the N-terminal and a CARD domain at the C-terminal. ASC recruits caspase-1 containing the CARD domain via CARD-CARD interactions to form inflammasome. ASC deficiency led to increased IFN production during DNA virus infection [57]. The CARD domain of ASC in AIM2 inflammasome was recently found to bind to the N-terminal domain of STING, thereby inhibiting the interaction of STING with TBK1 and thus negatively regulating the cGAS-STING signaling pathway [34]. NLRC3 protein containing the CARD domain blocked *type I* IFN response and IL-1β secretion by competing with ASC for caspase-1 binding, disrupting ASC speck formation, and interfering with NLRP3 inflammasome assembly and activation [63]. ASC in myeloid-derived macrophages and dendritic cells inhibited the interaction of STING with downstream TBK1, thereby reducing the induction of *type I* IFN [34]. Interestingly, a negative correlation between ASC expression and IFN-β levels was also observed in tuberculosis patients [34]. In summary, the CARD domain of ASC is essential for regulating the cGAS-STING signaling pathway (Fig. 1).

Nod-like acceptors (NLRs) regulate cGAS-STING

Except as described above, there are various other inflammasomes, such as NLRX1, NLRP2, NLRC3, NLRC4, NLRC5, NLRP6, NLRP12 [64–70]. Recent studies have shown the emerging roles of NLRs in the cGAS-STING signaling pathway. Most NLRs positively influence inflammatory responses, particularly the inflammasome NLRs. However, emerging studies have revealed that NLRC3 negatively affect *type I* IFN response by sequestering and attenuating STING activation [63, 67, 68]. NLRC3 binds viral DNA and other nucleic acids via its LRR domain, which enhances the ATPase activity of nucleic acids. Furthermore, the ATP binding by NLRC3 reduces its interaction with STING, resulting in decreased production of IFN-β and IL-6 [67, 68]. NLRC3 also interacts with pro-caspase 1 and ASC through its CARD domain, thereby preventing the formation of NLRP3 and NLRC4 inflammasomes and further inhibiting cell pyroptosis [63]. Similar to NLRC3, NLRX1 interacts with STING through its nucleotide-binding domain (NBD), which results in a block of STING-TBK1 interaction thereby inhibiting TBK1 activation required for *type I* IFN production [69]. NLRP2 directly interacts with TBK1, disrupting the TBK1-IRF3 interaction and interfering with TBK1-induced IRF3 phosphorylation, thereby inhibiting IFN signaling [70]. NLRP4 negatively modulates *type I* IFN signal transduction through activation of TBK1, which is degraded by K48-associated ubiquitination by the E3 ubiquitin ligase DTX4 [71]. NLRP11 limits *type I* IFN activation by impairing TBK1-induced IFN-β promoter activity, suggesting its potential involvement in the cGAS-STING signaling pathway [72]. NLRP14 physically interacted with STING components and facilitated the ubiquitination and degradation of TBK1, which mediated the interactions and inhibitory function [73]. NLRP6 binds viral RNA via RNA helicase Dhx15 and interacts with MAVS (mitochondrial antiviral signaling) to trigger the production of *type I* IFN [74]. NLRC4 promotes the cGAS-STING pathway by enhancing TBK1 interaction with the E3 ubiquitin ligase CBL to promote K63-linked polyubiquitination and subsequent activation of TBK1 [75, 76]. Furthermore, NLRC5 has the ability to stimulate the production of *type I* IFN and pro-inflammatory cytokines by fibroblasts and primary human cells when infected with cytomegalovirus or Sendai virus [77, 78].

cGAS-STING regulates inflammasomes and pyroptosis

cGAS-STING regulates NLRP3 inflammasome and pyroptosis

The cGAS-STING-NLRP3 signaling pathway is a specific mechanism that facilitates the activation of the NLRP3 inflammasome and the secretion of IL-1β in response to DNA virus infection and cytoplasmic DNA stimulation (Fig. 2). In human myeloid cells, the cGAS-STING pathway was necessary for cytoplasmic DNA-induced NLRP3 activation during viral and bacterial infection [79]; similarly, studies have shown that the STING-NLRP3 axis is critical for the pro-inflammatory response induced by *Chlamydia trachomatis* and aged macrophages [80, 81]. Furthermore, STING-IRF3 could trigger LPS-induced cardiac dysfunction, inflammation and pyroptosis by activating NLRP3 in mice [82]. In addition, in septic mouse neutrophils, downregulation of NAT10 inhibited ULK1 expression, activated the cGAS-STING pathway, induced NLRP3 inflammasome activation, and thus promoted neutrophil pyroptosis [83]. Moreover, the cGAS-STING pathway was activated in myelodysplastic syndromes (MDS) to induce IFN-stimulated genes (ISG), which triggered the activation of NLRP3 inflammasome [84].

During viral and bacterial infections in human myeloid cells, NLRP3 was tightly linked to the upstream cGAS-STING pathway, inducing NLRP3 inflammasome activation and coordinating lysosomal cell death (LCD) in a K^+ efflux-dependent manner [79]. Cytoplasmic DNA was recognized by cGAS, and then STING was activated and transported to the lysosome, triggering membrane permeation and causing LCD [85]. Lysosomal lysed cathepsin leaked into the cytoplasm, altered plasma membrane permeability, activated K^+ efflux upstream of NLRP3

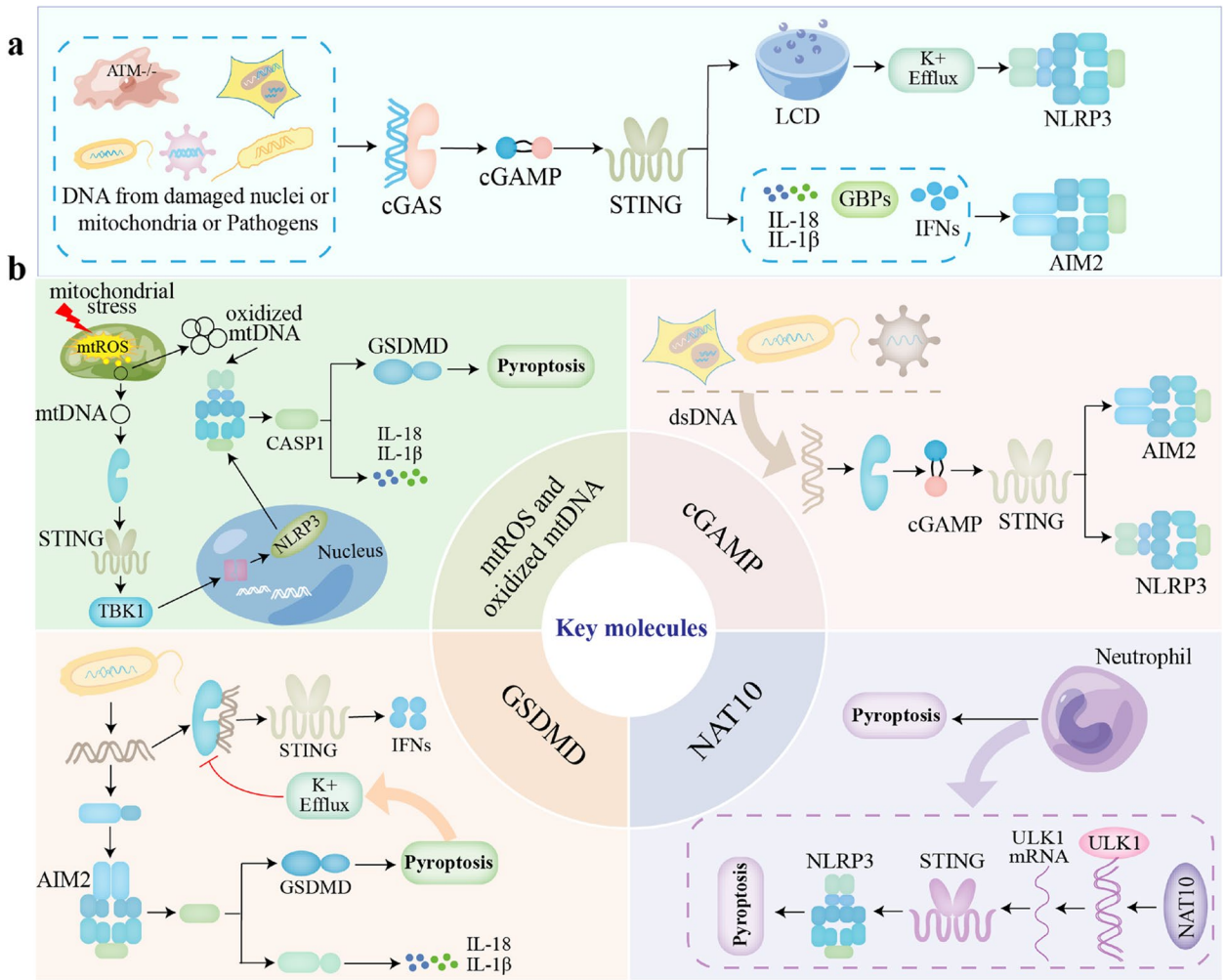

Fig. 2 cGAS-STING regulates inflammasomes and pyroptosis, and the key molecules in the crosstalk network of cGAS-STING, inflammasomes, and pyroptosis (**a**) cGAS-STING regulates AIM2 inflammasome, NLRP3 inflammasome, and pyroptosis. (**b**) the key molecules, including ox-mtDNA, mtROS, GSDMD, NAT10, ULK1, and cGAMP, in the crosstalk network of cGAS-STING, inflammasomes, and pyroptosis

and ultimately induced pyroptosis [79], which triggered a series of inflammatory cascade responses. In summary, DNA-triggered the NLRP3 inflammasome activation is dependent on the cGAS-STING-LCD axis, and targeting this pathway would ameliorate the inflammatory response associated with cytoplasmic DNA receptor evocation.

Available studies indicate that STING interaction with NLRP3 in response to cytoplasmic DNA stimulation promotes NLRP3 inflammasome activation in several ways. Firstly, STING recruited NLRP3 to promote its localization in the ER, thereby promoting the formation of NLRP3 inflammasome [86]. Secondly, TM5 (151-160aa) of STING interacted with NACHT and LRR domain in NLRP3 to attenuate NLRP3 polyubiquitination associated with K48 and K63, i.e., STING deubiquitinated NLRP3 to activate the NLRP3 inflammasome [86]. Thirdly, in an epistatic regulatory mechanism study, H3K4-specific histone methyltransferase WDR5 and H3K79 methyltransferase DOT1L inhibitors were found to significantly reduce STING overexpression-mediated NLRP3 upregulation, suggesting that STING promoted NLRP3 promoter region histone methylation via WDR5/DOT1L, thereby recruiting IRF3 to increase NLRP3 transcription [87].

cGAS-STING regulates AIM2 inflammasome

AIM2 is the only member of the PYHIN gene family that is truly homologous between mouse and human [88], and gain-of-function and loss-of-function studies at the cellular level have shown that human AIM2 functions in the same way as its mouse counterpart,

AIM2 [89]. Thus, studies of AIM2 in the mouse system can be extrapolated to humans. AIM2, an innate sensor of the canarypox virus vector ALVAC, triggers inflammasome activation in human and mouse antigen-presenting cells. CRISPR/Cas9 analysis reveals that ALVAC activated the AIM2 inflammasome through stimulation of the cGAS-IFI16-STING-type I IFN pathway [90]. Cytoplasmic DNA in ataxia-telangiectasia mutated (ATM)-deficient microglia was sensed by cGAS, thereby activating the cGAS-STING pathway to initiate an antiviral response, and triggering the activation of the AIM2 inflammasome [91]. Activation of the STING pathway during *Francisella* infection promoted *type I* IFN production and IRF1 expression, which induced guanylate-binding proteins (GBPs) targeting bacterial vesicles to disrupt their membranes, allowing bacterial products to be sensed by AIM2 and subsequently activating the AIM2 inflammasome [92]. The STING-dependent *type I* IFN signaling pathway was essential for the GBP-mediated release of *Brucella* DNA into the cytosol and the subsequent activation of AIM2 [93]. Collectively, these data indicated that the STING signaling axis-induced *type I* IFN is necessary for therelease of cytoplasmic DNA for activation of the AIM2 inflammasome (Fig. 2).

Chlamydia trachomatis replication or metabolism induced *type I* interferon responses are critical mediators of inflammasome activation and pyroptosis in macrophages [80]. cGAS-STING-dependent TNF and IFN signaling triggers necroptosis in response to cytosolic DNA [94]. In addition, mtDNA activates the STING pathway that subsequently enhances RIPK3/MLKL expression to trigger necroptosis [95]. Emerging evidence suggests that ER stress associated with STING activation can trigger apoptosis [96–98]. Therefore, cGAS-STING signaling can trigger multiple cell death pathways including pyroptosis, apoptosis, and necrosis, and a better understanding of the regulatory mechanisms across different cell types, states and health, and environmental and/or stimulus-dependent mechanisms will require further investigation. In addition, the key role played by the cGAS-STING signaling pathway in multiple cell death pathways, such as the newly described PANopoptosis, ferroptosis, and cuproptosis, remains to be thoroughly investigated and explored. Further mechanistic elucidation will help answer questions such as what determines the bidirectional regulation of cGAS-STING and cell death pathways. More importantly, the answers to these critical questions will provide new ways and methods to target the cGAS-STING-mediated cell death pathways for the treatment of infectious diseases, inflammatory diseases, and so on.

Key molecules in the crosstalk network of cGAS-STING, inflammasomes, and pyroptosis

Ox-mtDNA and mtROS

Mitochondria regulates the innate immune system through the release of numerous pro-inflammatory signals, such as mitochondrial reactive oxygen species (mtROS), mitochondrial DNA (mtDNA) and Ca^{2+}, which is vital for the inflammasomes and cGAS-STING pathways activation (Fig. 2) [99–102]. Exposure of newly synthesized mtDNA to ROS induces oxidized mtDNA (Ox-mtDNA) production [103]. Ox-mtDNA was either repaired by 8-oxoguanine-DNA glycosylase (OGG1) or cleaved into 500–650 bp fragments by flap-structure-specific endonuclease 1 (FEN1). These fragments leaked from the mitochondria via 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (mPTP)- and voltage-dependent anion channel (VDAC)-dependent channels and triggered NLRP3 inflammasome activation in the cytoplasm [104]. Ox-mtDNA fragments also led to phosphorylation of the STING Ser365 site, which was required for cGAS-STING-IRF3 binding and activation of the *type I* IFN response [104]. Brown adipose tissue (BAT) acts as an important thermogenic organ, regulating energy metabolism through thermogenesis [105–107]. BAT inflammation is associated with mitochondrial dysfunction and impaired thermogenesis [108–110]. mtROS was scavenged by mitochondrial thioredoxin-2 (TRX2), and TRX2 deficiency induced massive mtROS production, mitochondrial integrity disruption, and cytosolic release of mtDNA, which activated aberrant innate immune responses in BAT, including the cGAS-STING and the NLRP3 inflammasome pathways [111].

XBP1 deficiency induced the excessive production of ROS to promote hepatocyte pyroptosis through the activation of NLRP3 and pyroptosis signaling, which made it easier to release the mtDNA into the extracellular space. mtDNA released from thioacetamide (TAA)-stressed hepatocytes was engulfed by macrophages, further inducing cGAS- and dose-dependent macrophage STING activation [112]. The mitochondrial oxidative stress response also plays a role in bacterial infection. Mitochondrial oxidative stress-induced release of mtDNA in bacterial infection mediated the secretion of *type I* IFNs via the cGAS-STING pathway and triggered activation of the NLRP3 inflammasome [113, 114]. *Mycobacterium abscessus* facilitated the production of Ox-mtDNA to enhance cGAS-STING-dependent IFN production and NLRP3 inflammasome-mediated IL-1β [115]. Intracellular mtROS/mtDNA induced bacterial replication after phagosome rupture and escaped into the cytoplasm, disrupting membrane integrity in a *type I* IFN-dependent manner [115]. *Type I* IFN, on the other hand, inhibited NLRP3 inflammasome activation via the STAT pathway

[116, 117]. In addition, *type I* IFN-mediated generation of nitric oxide synthase (iNOS) and NO inhibited NLRP3 protein oligomerization, thereby preventing the assembly of NLRP3 inflammasome [118].

GSDMD

GSDMD not only promotes the effective release of IL-1β and IL-18, but also acts as an end-effector of pyroptosis. Another function of GSDMD is to promote the non-selective release of K^+ in cells. During infection with *F. novicida*, cGAS-induced IFNs were inhibited by GSDMD-mediated K^+ efflux, and GSDMD deficiency was found to prevent cytoplasmic K^+ efflux and enhance dsDNA binding to cGAS, thereby activating the cGAS-STING pathway and promoting IFNs secretion [62], suggesting that GSDMD inhibits cGAS mediated IFNs secretion. Furthermore, given the central role of the cGAS pathway in the innate immune response, it is expected that various modulations and modifications to cGAS control its activity. Further studies indicates that members of the tripartite motif 56 (TRIM56) induced the Lys335 monoubiquitination of cGAS, which resulted in a marked increase of its dimerization, DNA-binding activity, and cGAMP production of cGAS [119, 120]. In summary, bacterial dsDNA triggers the activation of inflammasomes, leads to GSDMD cleavage, and causes K^+ efflux, thereby limiting the binding of bacterial dsDNA to cGAS, inhibiting the activation of the cGAS-STING pathway, and disrupting the inflammatory response of IFNs (Fig. 2).

NAT10 and ULK1

As the first identified RNA acetyltransferase, N-acetyltransferase 10 (NAT10) catalyzes the N4 acetylation of cytidine (ac4C) to regulate mRNA stability and translation, and is implicated in a variety of cellular processes including cell division, cellular senescence, autophagy and DNA damage [121, 122]. Neutrophils play an important role in the progression of sepsis as major effector cells against infection and as important regulators of innate immunity [123]. During sepsis, large amounts of bacterial products (e.g., CpG DNA) as well as the host's own DNA (including nuclear and mitochondrial DNA) were released into the cytoplasm, leading to the activation of cGAS-STING and pyroptosis [124]. NAT10 was a negative regulator of neutrophil pyroptosis, and its reduced expression led to increased neutrophil pyroptosis and secretion of large amounts of the pro-inflammatory cytokines IL-1β and IL-18 [83]. In neutrophil, down-regulation of NAT10 led to a decrease in UNC-52-like kinase 1 (ULK1) expression level. In contrast, as a regulator of STING phosphorylation, deletion of ULK1 activated the STING-IRF3 pathway, which subsequently triggered NLRP3 inflammasome activation and neutrophil pyroptosis [125]. On the other hand, ULK1 has been shown to be involved in NLRP3 autophagy, suggesting that ULK1 has a direct regulatory effect on the NLRP3 inflammasome in addition to inhibiting STING (Fig. 2) [126].

cGAMP

cGAMP, as a second messenger, directly binds to STING and its upstream key synthetase cGAS, which further activated TBK1, induced IRF3 and NF-κB into the nucleus, produced *type I* IFN and cytokines, and defended against various viral infections. Studies showed that cGAMP increased the activation of AIM2 and NLRP3 inflammasomes via cGAS-STING (Fig. 2). cGAMP induced the activation of AIM2 and NLRP3 inflammasomes in addition to *type I* IFN by increasing mRNAs encoding key components of the inflammasome (AIM2, NLRP3, Casp1, IL-1β, and ASC), thereby inhibiting DNA virus infection [127].

Diseases induced by the crosstalk network of cGAS-STING, inflammasomes, and pyroptosis

A well-coordinated immune response is essential for recognizing and eliminating threats from foreign substances and tissue damage. However, uncontrolled inflammation can contribute to the pathology of chronic inflammatory and degenerative diseases, as well as cancer. Chronic inflammation plays a prominent role in driving carcinogenesis, as various chronic inflammatory conditions are associated with an increased risk of cancer. This leads to the accumulation of DNA damage and production of local inflammatory cytokines. Eventually, the phenotype shifts towards an altered homeostasis and becomes irreversibly responsive to continued inflammation, resulting in malignancy [128–130]. Recent studies support the idea that inflammation influences the fate of various components within the complex tumor microenvironment, ultimately creating a tumor-promoting environment through reciprocal communication that promotes carcinogenesis either through direct mutagenesis or by activating cytokine responses that effectively shape the host response [128, 131].

There is increasing evidence that the risk of developing chronic inflammation can be traced back to early development, and its consequences are now known to extend throughout the life span, affecting health and mortality risk in adulthood [132–134]. Therefore, the "inflammatory fire" sparked by the host response requires tight management to avoid spreading and causing irreversible damage. Recent evidence has demonstrated that activation of the cGAS-STING axis in response to cytosolic DNA stimulation engaged

in inflammasome activation [79, 86] and GSDMD-triggered pyroptosis [135], which is characterized by the dysfunctions of the immune system and the aberrant secretion of inflammatory cytokine. As a result, the interplay among the cGAS-STING axis, inflammasome, and pyroptosis builds a wide range of important monitoring systems in response to tissue damage and pathogen invasion. Abnormalities of this crosstalk cause a variety of human diseases, including infectious diseases, autoimmune diseases, tumors, organ fibrosis and neurodegenerative diseases [11, 136–138]. In view of the critical role of cGAS-STING, inflammasomes and pyroptosis in immune and inflammatory responses, we then focused on the related diseases induced by this crosstalk network with the aim of providing clues for their prevention and treatment (Fig. 3).

Cardiac dysfunction

cGAS-STING pathway can activate the NLRP3 inflammasome, thereby exacerbating inflammation in the myocardium and promoting cardiac dysfunction. In cardiomyocytes, STING binds to IRF3 and phosphorylates IRF3, which subsequently translocated into nucleus and increased the expression of NLRP3 [82]. In contrast, STING knockdown inhibited IRF3 phosphorylation and perinuclear translocation, thereby suppressing NLRP3-mediated cardiomyocyte inflammation and pyroptosis, improving cardiac function and increasing survival [82]. Also, in diabetic cardiomyopathy (DCM), the production of free fatty acids induced oxidative mitochondrial damage, activated the cGAS-STING and NLRP3 inflammasome signaling pathways, and ultimately promoted myocardial hypertrophy in DCM by promoting cardiomyocyte pyroptosis [139]. Activation of STING

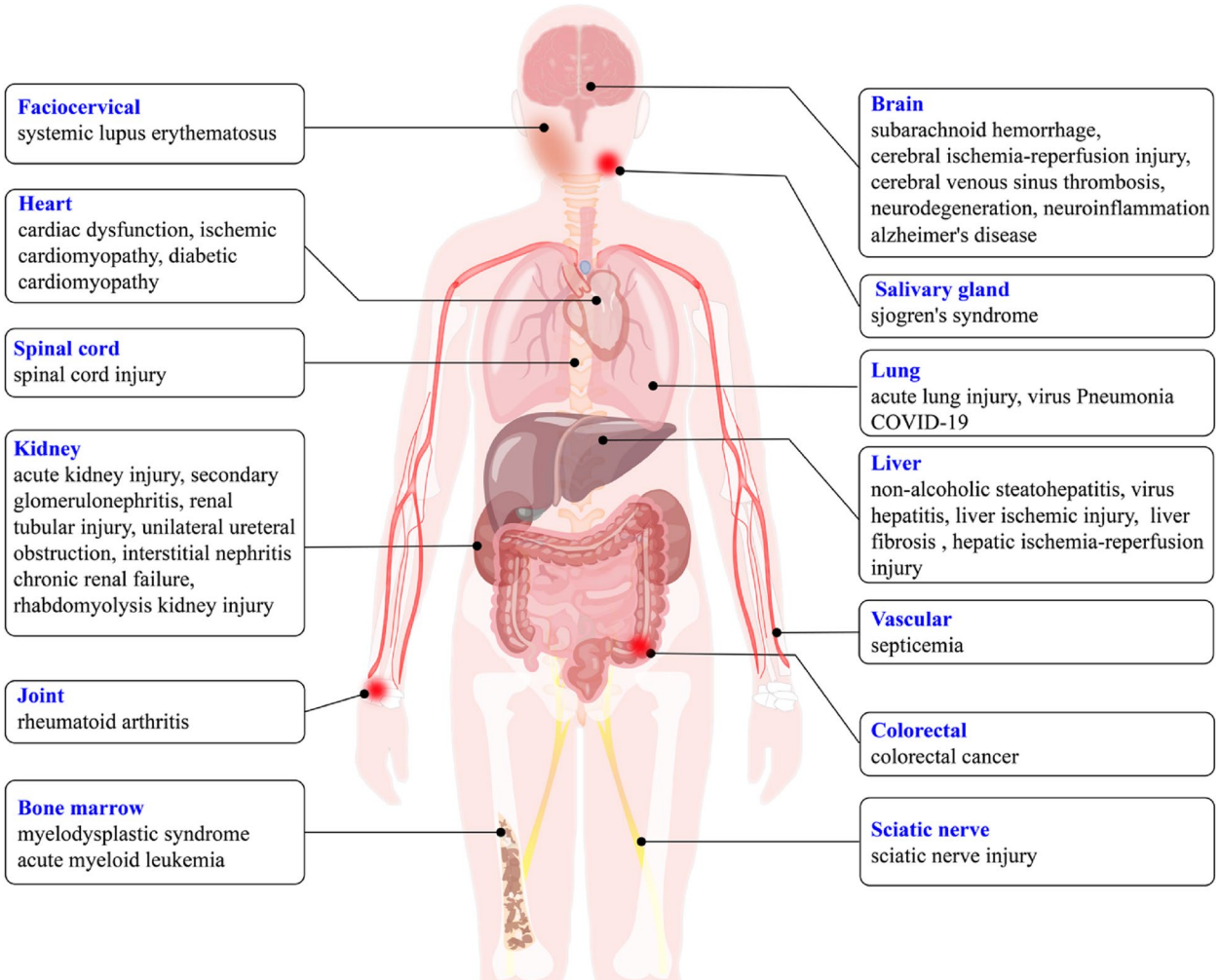

Fig. 3 Diseases induced by the crosstalk network of cGAS-STING, inflammasomes, and pyroptosis. Evidence shows that the crosstalk network of cGAS-STING, inflammasomes, and pyroptosis is involved in the pathogenesis of a number of diseases, such as lung diseases, liver diseases, kidney diseases, cardiac dysfunction, spinal injury, arthritis, nervous system diseases, autoimmune diseases, and malignant tumors

enhanced GSDMD-mediated cardiac hypertrophy [140]. Consistently, knock down cardiomyocyte STING in DCM attenuated cardiac pyroptosis and inflammatory responses, suppressed DCM-induced cardiac hypertrophy, and restored cardiac function [139]. Therefore, targeting cardiomyocyte STING, NLRP3 inflammasome, and pyroptosis may be a potential therapeutic strategy to prevent cardiomyopathy.

Acute lung injury (ALI)

Macrophages are the most abundant immune cells in lung tissue, and inhibition of inflammatory signaling pathways in macrophages is essential to maintain tissue homeostasis. Macrophages are more likely to exhibit cellular senescence, impaired mitochondria, and abnormal activation of the cGAS-STING and NLRP3 inflammasome pathways, which predispose mice to severe viral pneumonia during infection [141]. Cytoplasmic mtDNA and STING transcription factor (c-Myc) synergistically activated the cGAS-STING pathway in LPS-induced ALI, which subsequently exacerbated ALI inflammation by triggering NLRP3 inflammasome activation and pyroptosis [142, 143]. The STING agonist diamidobenzimidazole (diABZI), was internalized into the cytoplasm and induced STING activation and dimerization, and upregulated apoptosis, pyroptosis and necroptosis (PANoptosis), which enhanced lung inflammation with severe acute respiratory distress syndrome [144]. Radiation therapy-induced self-dsDNA was leaked into the bronchoalveolar space and subsequently triggered cGAS-STING activation and downstream NLRP3-mediated pyroptosis, providing a mechanistic basis for pyroptosis that connects cGAS-STING activation to the exacerbation of initial radiation-induced lung injury [145]. In summary, the cytoplasmic cGAS-STING-NLRP3 pathways contribute to LPS-induced ALI. Based on these findings, targeting the cytoplasmic cGAS-STING-NLRP3 pathways may be a therapeutic target for ALI.

Liver diseases

The liver is a prime target for toxins and acute injury as the primary organ for removal of various drugs and foreign pathogens. Macrophage infiltration is a characteristic of liver inflammation, and macrophage activation of the cGAS-STING and inflammasome pathways are important drivers of numerous liver diseases [146–149]. Increased STING activation was observed in human and mouse liver with nonalcoholic steatohepatitis [150, 151]. Macrophage STING activation in acute ischemic liver injury facilitated by mtDNA release from injured hepatocytes [81]. Ox-mtDNA produced under oxidative stress of liver injury triggered the activation of NLRP3 inflammasome [152]. Experimental CCl_4 induced liver fibrosis and enhanced cGAS-STING activation in liver tissue, while STING deficiency attenuated liver inflammation and fibrosis [153–155]. RNA sequencing of livers from mice with CCl_4-induced liver fibrosis revealed that the STING and NLRP3 inflammasome signaling pathways were activated during liver fibrosis, and the activation of these two pathways were also verified in human and mouse cirrhotic tissues [87]. STING and NLRP3 signaling pathways are activated in cirrhosis, and both knockdown of STING and STING inhibitor C-176 significantly inhibited NLRP3 expression and hepatocyte pyroptosis [87], suggesting that STING can induce hepatocyte pyroptosis through activation of the NLRP3 inflammasome.

GSDMD-mediated hepatocyte pyroptosis contributes to accelerated pathogenesis in acute and chronic liver disease [156–159]. In mice, activation of the NLRP3 inflammasome resulted in hepatocyte pyroptosis, hepatic inflammation, and liver fibrosis [158]. In addition, caspase-1 and GSDMD-mediated hepatocyte pyroptosis induced stellate cell activation through the release of inflammatory factors, thereby promoting the development of liver fibrosis [159]. STING induced hepatic ischemia-reperfusion injury (IRI) by promoting calcium-dependent caspase-1-GSDMD in macrophages, and STING expression enhanced with increased hepatic IRI, while knockdown of STING attenuated hepatic IRI [160]. ROS also plays a key role in hepatocyte pyroptosis [161, 162]. Upregulation of ROS levels promoted GSDMD cleavage, activated the GSDMD-N terminus, and induced cell membrane pore formation, thereby promoting pyroptosis [163, 164]. In addition, in TAA-induced liver injury, hepatocyte ROS-NLRP3-caspase-1-GSDMD activity was increased and hepatocyte pyroptosis was detected [112]. XBP1 deficiency in hepatocytes promoted ROS production to activate NLRP3-Caspase-1-GSDMD signaling, which promoted extracellular release of mtDNA and macrophage phagocytosis of mtDNA, further activated the cGAS-STING pathway, thereby promoting hepatocyte pyroptosis [112].

Kidney diseases

Acute kidney injury (AKI) is marked by a progression of rapid loss of kidney function that can lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD) [165, 166]. Recent studies suggest that mtDNA-associated chronic inflammatory responses are associated with the pathogenesis of AKI and the development of CKD [167–169]. Mitochondrial damage was induced in AKI, leading to leakage of mtDNA into the cytoplasm and activation of the cGAS-STING pathway, which phosphorylated TBK1 and IRF3, promoted the secretion of inflammatory factors and exacerbated the inflammatory response [168]. Activation of the cGAS-STING pathway

was observed in multiple AKI mouse models and AKI patients [168, 170, 171]. STING knockout mice exhibited reduced renal function, tubular damage and inflammation after cisplatin treatment [168]. In addition, STING mediated secondary renal inflammation and tubular injury. STING and NLRP3 inflammasome pathways played important roles in unilateral ureteral obstruction, adenine-induced tubulointerstitial nephritis and chronic renal failure [172–174]. Expression of G2-type apolipoprotein APOL1 (G2 APOL1) in mouse kidney cells led to activation of cGAS-STING and NLRP3 inflammasome, and APOL1 expression correlated with caspase-1 and GSDMD levels [175]. In a RIAKI mouse model, although AIM2 deficiency inhibited renal macrophage pyroptosis, it surprisingly accentuated abnormal inflammation as evidenced by massive macrophage aggregation ($CXCR3^{+}CD206^{+}$) and activation of the cGAS-STING-TBK1-IRF3 pathway, which subsequently promoted maturation and secretion of pro-inflammatory cytokines. Meanwhile, dsDNA-induced AIM2-deficient cells escaped rapid pyroptotic elimination and participated in STING-TBK1-IRF3/NF-κB pathways, leading to an exacerbation of the inflammatory phenotypes [33]. These finding suggested that the rapid macrophage cell death induced by dsDNA may serve as an anti-inflammatory program and may determine the healing process of RIAKI.

Nervous system inflammation

Microglia are important mediators of neuroinflammation and immune response after CNS injury [176, 177]. NLRP3 inflammasome-mediated microglia pyroptosis is associated with the pathogenesis of subarachnoid hemorrhage [178], cerebral ischemia/reperfusion injury [179, 180], and spinal cord injury [181]. Recent studies have shown that cytoplasmic DNA induces NLRP3 and AIM2 inflammasomes activation and GSDMD-triggered microglia pyroptosis through activation of the cGAS-STING pathway [79, 86, 91, 135]. Importantly, elevation in cGAS and STING occurred mainly in microglia in damaged cortex after cerebral venous sinus thrombosis (CVST), and the same cellular localization was reported in cerebral ischemia/reperfusion (I/R) [135] and subarachnoid hemorrhage models [5]. Accumulation of dsDNA on cell membranes triggered activation of cGAS-STING pathway in intracranial venous and CVST, which subsequently induced NLRP3 inflammasome activation, microglia pyroptosis, and increased the neuroinflammatory burden [182]. Hyperphosphorylated Tau in the brain is an important pathological feature of patients with neurodegenerative diseases. Tau induced NLRP3 inflammasome activation, which drived tau hyperphosphorylation and exacerbated neuroinflammation, and the biological process may be attributed to the immune stimulating activity, especially the cGAS-STING pathway [183–185]. The STING agonist CMA significant increased STING expression in microglia after subarachnoid hemorrhage (SAH) and exacerbation of neuronal damage [5]. In addition, in the brains of patients with different neurodegenerative diseases, serum/glucocorticoid-related kinase 1 (SGK1) was elevated. SGK1 expression is widely detected in the brain, and it is increased in pathologic conditions such as Rett syndrome [186], Alzheimer disease (AD) [187, 188], multiple sclerosis [189], amyotrophic lateral sclerosis [190], and neuropathic pain [191], collectively suggesting that SGK1 plays pathogenic roles in neurodegenerative disorders. Inhibition of glial SGK1 corrects the pro-inflammatory characteristics of glia by reducing intracellular NF-κB, NLRP3 inflammasome and cGAS-STING mediated inflammatory pathways [192]. Activation of the cGAS-STING pathway in AD mice triggered the formation of NLRP3 inflammasome, exacerbated cellular senescence and inflammatory responses, and nicotinamide riboside (NR) treatment exerted beneficial effects through the cGAS-STING pathway [193]. Furthermore, inflammatory response-induced microglia activation was associated with neurological deficits after traumatic brain injury (TBI). In contrast, microglia cGAS-STING activation promoted neuroinflammatory responses after TBI, in part through activation of the NLRP3 inflammasome [194]. In conclusion, the cGAS-STING-NLRP3 signaling pathway may serve as a potential therapeutic target for neuroinflammation-induced neurological dysfunction.

Myelodysplastic syndrome (MDSs) and spinal injury (SCI)

NLRP3 inflammasome, pyroptosis and cGAS-STING contribute to neuroinflammation in myelodysplastic syndromes (MDSs) and spinal cord injury (SCI) [84, 195]. cGAS-STING induced activation of interferon-stimulating factor (ISG), triggered NLRP3 inflammasome activation, and exacerbated bone marrow injury [84]. Further studies revealed that caspase-1 degraded the erythroid transcription factor GATA-binding protein 1, triggering anemia and myeloid bias to exacerbate the injury [84]. MDSs hematopoietic stem and progenitor cells (HSPCs) overexpressed inflammasome proteins and exhibited NLRP3 inflammasomes activation that directly produced IL-1β and IL-18, and drived pyroptosis [196]. As with somatic mutations, excess alarm protein S100A9 in bone marrow plasma activated NADPH oxidase (NOX), increased ROS levels, exposed cytoplasmic DNA to the cGAS-STING-NLRP3 axis, and promoted pyroptosis [196]. In addition, cGAS-STING and NLRP3 inflammasome activation in spinal microglia after sciatic nerve injury have been shown to exacerbate neuroinflammation in mice [195]. cGAS, STING, and NLRP3 were correlated

with the extent of intervertebral disc degeneration by magnetic resonance imaging (MRI) and histopathology. Oxidative stress initiated the STING-dependent activation of the cGAS-STING axis and NLRP3-inflammasome-mediated pyroptosis in human nucleus pulposus cells [197]. Taken together, these data implicate the essential role of the cGAS-STING-NLRP3 axis and pyroptosis in the development of IVD degeneration and offer a potential treatment approach for the management of discogenic low back pain.

Autoimmune diseases

Activating the cGAS-STING pathway confers host immunity and contributes to eliminating multiple pathogens, including viruses and bacteria. Meanwhile, excessive STING and inflammasome activation have been identified as contributing to the progression of autoinflammatory diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), acute myeloid leukemia (AML), sepsis and dry syndrome [83, 195, 198–202]. During SLE, STING and NLRP3 inflammasome activation mediated caspase-1 activation and promoted maturation and secretion of inflammatory factors [198, 199]. In addition, monocytes in SLE patients showed considerable activation of caspase-1 [200]. In acute myeloid leukemia (AML) with TP53 mutations, the therapeutic agent DNA methyltransferase inhibitors (DNMTis) expressed endogenous retroviruses (ERVs), IFNs and activated NLRP3 inflammasome in a STING-dependent manner [201]. DNA polymerase β (Pol β) was significantly decreased in peripheral blood mononuclear cells (PBMCs) of RA patients and mice with collagen-induced arthritis (CIA). Further studies revealed that Pol β knockdown led to DNA damage accumulation and cell membrane dsDNA leakage, which activated the cGAS-STING-IRF3-NF-κB signaling pathways and promoted pyroptosis [202].

Malignant tumors

Growing evidence indicates that the innate immune response is critical to tumorigenesis and antitumor therapy [130, 203]. In mouse models and clinical patients, activation of the cGAS-STING pathway has been proven to reduce tumor growth and improve immunogenicity [204]. STING enhanced IL-18 and IL-1β generation by macrophages by activation of NLRP3, and IL-18 and IL-1β induced 4-1BBL and 4-1BB expression in macrophages and NK cells, respectively, which facilitated macrophage STING signaling to improve anti-tumor function, thus suppressing colorectal cancer liver metastasis [205]. Macrophage STING signaling pathway promoted NLRP3 inflammasome activation, enhanced anti-tumor function of NK cells, and inhibited liver metastasis from colorectal cancer [206]. However, cGAS-STING activation-mediated chronic inflammation can also promote tumor metastasis through the induction of immunosuppressive TME [9]. Cancer cell-produced cGAMP enhanced tumor growth and chemoresistance through activation of astrocyte STING and production of inflammatory cytokines [207].

COVID-19

Severe COVID-19 is characterized by an excessive inflammatory response, including large cytokine expression, that involves a wide range of immune cells, including macrophages and neutrophils, that sense pathogens and damaged autologous structures and subsequently induce the production of inflammatory mediators. Infection and replication of SARS-CoV-2 in immune cells within the lung is a key driver of the disease. Inflammasome activation and the accompanying inflammatory response are necessary for lung inflammation in COVID-19 [208–211]. The cGAS-STING pathway, which controls immunity to cytosolic DNA, is a critical driver of aberrant *type I* IFN responses in COVID-19 [212, 213]. SARS-CoV-2 infection has a dual-edged sword effect on STING signaling, relying on the progressive stage of the disease and the infected tissue. Therefore, STING agonists or inhibitors are promising for the prevention and treatment of SARS-CoV-2. For example, STING agonists are used in the early stage of infection to activate the immune response in the body to kill the virus and inhibit its replication, and STING inhibitors are used in the middle and late stages of infection to reduce the excessive immune response of the body and reduce lung inflammation [212–216]. However, the specific application of STING modulators in the prevention and treatment of COVID-19 still needs further research, including the specific timing of administration and medication standards.

Although the interaction network between the inflammasome and cGAS-STING pathways has not been reported during COVID-19 infection, we have reasons to believe that there is an inseparable close relationship and feedback regulatory mechanism between the two. On the one hand, SARS-CoV-2 infection induces inflammasome activation and triggers multiple cell death pathways including pyroptosis, apoptosis, and necrosis, which may lead to the release of dsDNA in the nucleus and mitochondria into the cytoplasm under certain conditions. cGAS recognizes dsDNA without sequence difference and activates STING pathway to generate immune response. The continuous activation of the two pathways induces the production of a large number of inflammatory factors and aggravates the immune inflammatory response of the body. In addition, as mentioned in section 2, AIM2 inflammasome, AIM2-like receptors,

NLRP3, caspases, GSDMD, and CARD domain of ASC can all participate in regulating the activition of cGAS-STING signaling pathway. It can be seen that the crosstalk of inflammasome and cGAS-STING pathways has not yet been clarified in COVID-19 patients, and how the two interact and how to regulate the body's immunity are still key issues to be solved.

Regulators of the crosstalk network of cGAS-STING, inflammasome, and pyroptosis

As described above the crosstalk network of cGAS-STING, inflammasome and pyroptosis is correlated with an elevated risk of the development of a broad range of chronic diseases that are currently the leading cause of morbidity and mortality throughout the world and are responsible for an enormous amount of human suffering. At the same time, the discovery of regulators such as agonists, inhibitors, vaccines and physical factors that could be explored to enrich this work and convert this work into meaningful strategies for improving human health (Fig. 4).

Natural products

The cGAS-STING, inflammasome and pyroptosis pathways exacerbate the progression and course of various diseases through the crosstalk network, and therefore the search for their modulators is of great importance for disease prevention, treatment and recovery. Natural products are currently becoming an important source of drug discovery for disease treatment due to their broad pharmacological activity, high safety profile and diversity of targets.

4-Octylic acid (4-OI), an immunomodulatory derivative accumulated during macrophage activation, has attracted widespread attention for its anti-inflammatory and antioxidant properties. In vitro and in vivo experiments have shown that 4-OI inhibited the activation of the cGAS-STING-IRF3 pathway by eliminating mtROS production and mtDNA leakage in alveolar macrophages under oxidative stress, while alleviated LPS-induced NLRP3 inflammasome-mediated pyroptosis, which in turn ameliorated acute respiratory distress syndrome (ARDS) [217]. Epigallocatechin gallate (EGCG) is a catechin monomer isolated from tea and is a major component of green tea polyphenols. Advanced in vitro study that EGCG could block the activation of NLRP3 inflammasome through down-regulation of cGAS-STING-IRF3 pathway, and thus had significant protective effects against H_2O_2-induced apoptosis and inflammation in myeloid cells [218].

Several studies have shown that the physiologic concentration of hydrogen sulfide (H_2S) has a vital role in the cardiovascular system through the regulation of biological functions and the maintenance of homeostasis in the body [219, 220]. Conversely, the lack of endogenous H_2S is harmful and may lead to the development of various cardiovascular diseases, including atherosclerosis, hypertension, myocardial infarction and heart failure [221–223]. A high-choline diet reduced plasma H_2S levels and induced cardiac dysfunction via the cGAS-STING-NLRP3 inflammasome pathways, while H_2S treatment inhibited NLRP3 inflammasome activation mediated by cGAS-STING pathway activation, thereby restoring cardiac function [224]. As above discussed, the part of pathophysiological and pharmacological effects of H_2S have been demonstrated in vitro and in vivo studies as well as in clinical disease. However, accounting for these pathophysiological responses will not be easy in preclinical models of disease. Emodin is a natural bioactive compound from herbal medicine with anti-inflammatory, antioxidant, anticancer, hepatoprotective and neuroprotective effects. In vivo and in vitro studies showed that emodin protected hepatocytes from acetaminophen (APAP)-induced liver injury by upregulating Nrf2-mediated antioxidant stress response, inhibiting NLRP3 inflammasome and cGAS-STING-IRF3 pathways [225]. Urolithin A, one of the principal intestinal metabolites of ellagitannins, attenuated fructose-induced hyperuricemic nephropathy through the promotion of Parkin-dependent mitophagy, thus limiting the inflammatory response mediated by the STING-NLRP3 axis in vivo and in vitro experiments [226]. In summary, a variety of natural products have superior effects in regulating cGAS-STING, inflammasome and pyroptosis pathways, currently being investigated in vitro and in vivo, which should be explored in future research work to provide more diversified options for the treatment of related diseases.

Synthetic substance

Because of the significance of the STING pathway in the activation of innate immunity and the protection of the host against pathogens, targeting the innate immunity through STING agonists is a potential strategy for both antiviral and antitumor therapies [227, 228]. G10, a human-specific STING agonist, induced STING-dependent activation of both *type I* IFN and the canonical NLRP3 inflammasome in porcine cells [229]. The STING agonist diABZI resulted in cell death and self-DNA release, which was detected by cGAS and formed 2′3′-cGAMP, causing STING hyperactivation, amplifying the TBK1/IRF3 and NF-kB pathways, and subsequent secretion of IFN-I and inflammatory TNFα and IL-6. Meanwhile, the recognition of self-dsDNA or mtDNA by NLRP3 or AIM2 triggered the activation of the inflammasome, thereby leading to the cleavage of the GSDMD,

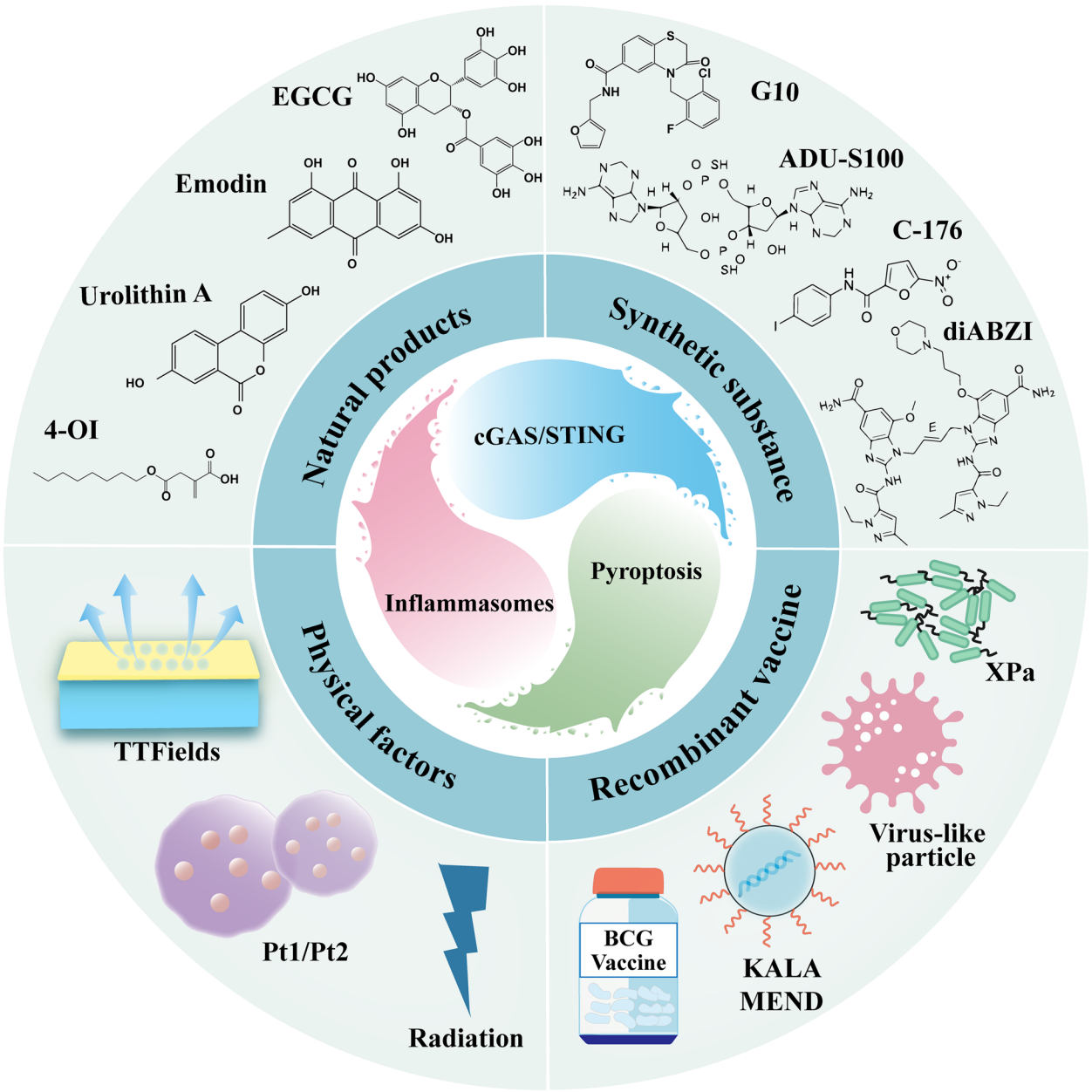

Fig. 4 Regulators of the crosstalk network of cGAS-STING, inflammasome, and pyroptosis The involvement of natural products (such as EGCG, emodin, urolithin A, and 4-Octylic acid), synthetic substances (such as G10, diABZI, ADU-S100, and C-176), recombinant vaccines (such as Xpa, BCG vaccine, KALA MEND, and virus-like particle), and physical factors (such as TTFields, Pt1/Pt2, and Radiation) in regulating the cGAS-STING, inflammasomes and pyroptosis pathways crosstalk network, providing potential candidates for the treatment of related diseases

allowing the formation of the GSDMD pore and the release of mature IL-1β and pyroptosis [144]. In traumatic brain injury (TBI), the use of the STING agonist ADU-S100 exacerbated the behavioral and pathological changes [194]. In addition, ADU-S100 promoted microglia activation and exacerbated pyroptosis-associated neuroinflammation by increasing caspase-1 cleavage as well as GSDMD-N-terminal expression [194]. However, administration of the STING antagonist C-176 attenuated TBI-induced inflammatory activation of microglia and reduced pyroptosis [194].

Recombinant vaccine

A low virulence, ESX-1 effective recombinant BCG vaccine (BCG::ESX-1Mmar) was developed by heterologous expression of the ESX-1 region in BCG, which

induced the cGAS-STING-type I IFNs axis and activated the AIM2 and NLRP3 inflammasomes, resulting in a higher proportion of $CD8^+$ targeting mycobacterial antigens shared with BCG^+ T cell effector ratio and specificity of $CD4^+$ Th1 cells against ESX-1 antigens [230]. In addition, pyroptosis of DCs via the cGAS-STING pathway and TLRs has recently been shown to be induced by a novel whole-cell inactivated *Pseudomonas aeruginosa* vaccine (XPa) [231]. Artificial nanoparticles, KALA-MENDs, delivered antigen-encoding plasmid DNA (pDNA) to antigen-presenting cells and promoted immune activation, suggesting their use as DNA vaccine vectors [232]. Further studies demonstrated that KALA-MENDs promoted IFN-β and IL-1β secretion through activation of the cGAS-STING pathway and induction of AIM2 and NLRP3 inflammasomes activation [232]. Similarly, a novel virus-like particle was effective at inducing cGAS binding, activating STING signaling, and generating *type I* IFN, and this virus-like particle also induced AIM2 inflammasome formation, GSDMD-mediated pyroptosis, and anti-tumor immunity [233].

Physical factors

The tumor treating fields (TTFields) is a therapy for the treatment of glioblastoma (GBM) and malignant mesothelioma. In addition, TTFields was found to induce nuclear membrane disruption in microglia, leading to release of large micronuclei from the cells, recruitment and activation of cGAS and AIM2 cytoplasmic DNA sensors, and ultimately leading to activation of the cGAS-STING pathway and the AIM2 inflammasome [234]. TTField-treated GBM cells induced anti-tumor memory immunity and resulted in 42 to 66% cure rates in a STING and AIM2-dependent manner [234]. PtII complexes, Pt1and Pt2, acted as photoactivators of the cGAS-STING pathway, disrupted the mitochondrion and nuclear envelope under light exposure, resulting in cytoplasmic leakage of mtDNA and activation of the cGAS-STING pathway to induce pyroptosis in tumor cells [235]. In addition, activation of the NLRP3 inflammasome and caspase-1 cleavage in macrophages may be promoted by radiation-induced ROS generation or mitochondrial damage [236]. Radiation-induced nuclear DNA leakage into the cytoplasm can be detected by cGAS-STING and activate the immune response; however, knockdown of NLRP3 over-activated the cGAS-STING pathway in macrophages and promoted pyroptosis and radiation-induced tissue damage in mice [237], suggesting that NLRP3 knockdown increases radiation-activated cGAS-STING-mediated IFN-β production, highlighting the importance of fine-tuned regulation.

Discussion and conclusion

Innate immune responses are rapid responses to disease agents or danger cues that are precisely timed to both effectively combat disease agents and limit excessive inflammation and tissue damage. However, overactivation of innate immunity has been shown to be detrimental and can lead to various diseases. The study of cGAS-STING, inflammasomes and pyroptosis is a rich area within immunology, with rapidly emerging insights into how it works and how to regulate. Due to the similarities in the cGAS-STING, inflammasomes and pyroptosis signaling pathways response to cellular stress and downstream effects, the main review in this paper focuses on their crosstalk network. NLRP3, AIM2 inflammasomes are able to antagonize the cGAS-STING signaling pathway. Upon activation of canonical and non-canonical inflammasomes, caspase-1 could also cleaves cGAS, indicating cross-regulation between intracellular DNA-sensing pathways. Moreover, the cGAS-STING pathway can also be regulated by disrupting the CARD domain of the linker protein ASC in the inflammasome complex. cGAS-STING acts as an important immune axis for microbial infection, chronic inflammation, cancer progression and organ degeneration [1, 9, 18, 238], and also regulates NLRP3, AIM2 inflammasomes.

The cGAS-STING signaling pathway interacts with AIM2 and NLRP3 inflammasome mainly caused by regulatory molecules such as Ox-mtDNA, mtROS, GSDMD, cGAMP and NAT10. mtDNA exposure to ROS induces Ox-mtDNA production, triggering intracytoplasmic NLRP3 inflammasome activation, leading to phosphorylation of STING, which activates the cGAS-STING signaling pathway. AIM2 senses bacterial dsDNA, triggers the formation of the AIM2 inflammasome, leads to the GSDMD cleavage to form membrane pores, thereby limiting bacterial dsDNA binding to cGAS, inhibiting cGAS-STING pathway activation. NAT10 is a negative regulatory factor of neutrophil pyroptosis and overexpression inhibits pyroptosis by blocking the ULK1-STING-NLRP3 pathways. On the other hand, ULK1 has been shown to be involved in NLRP3 autophagy, suggesting that ULK1 has a direct regulatory role on NLRP3 inflammasome in addition to STING inhibition. These key regulatory molecules are critical for the regulation of the crosstalk network of cGAS-STING, inflammasomes, and pyroptosis, and will also provide a strong reference for the selection of therapeutic targets.

Thus, modulating this innate immune system has the potential to treat a broad range of diseases, including infections, neurodegeneration, autoinflammation, metabolic disorders, and cancer. Recent studies have shown that the crosstalk network of cGAS-STING, inflammasomes, and pyroptosis exacerbates cardiac,

liver, lung, kidney, spinal cord, nervous system inflammation, induces autoimmune disease and promotes the progression of malignant tumors. While refinement of our understanding of cGAS-STING, inflammasome and pyroptosis continues, targeting of this crosstalk network as a therapeutic for multiple diseases is rapidly progressing. We therefore summarize the involvement of natural products, synthetic substances, recombinant vaccines, and physical factors in regulating the cGAS-STING, inflammasomes and pyroptosis pathways crosstalk network, providing potential candidates for the treatment of related diseases. As the epitome of precision medicine in inflammatory diseases, the continued profiling, refinement and re-purposing of direct and specific modulators will drive future clinical translation.

In summary, the cGAS-STING signaling pathway generates cascade amplification effects between inflammasomes, and pyroptosis, and activates immune inflammatory responses. On the one hand, the crosstalk of these signaling pathways can affect parenchymal organs such as heart, liver, lung, and kidney, and aggravate the development process of inflammatory diseases; in addition, it is also closely related to the progression of several autoimmune diseases. Therefore, further investigations are promising to uncover novel regulatory mechanisms that may provide new opportunities for therapeutic intervention in the exciting field of the crosstalk network of cGAS-STING, inflammasomes and the pyroptosis signaling axis.

Acknowledgements
Not applicable.

Authors' contributions
ZW, JL, and JT: Conceptualization; JL, JZ, and YL: Data curation; ZW: Funding acquisition; JL, XM, and XL: Investigation; ZW and JL: Methodology; JZ and YL: Resources; XM and JL: Software; ZW and JT: Supervision; JL and JT: Visualization; ZW and JL: Writing – original draft; JT and XM: Writing – review & editing.

Funding
This work has been supported by the National Natural Science Foundation of China (82204706), China Postdoctoral Science Foundation (2022MD723714).

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China. [2]TCM Regulating Metabolic Diseases Key Laboratory of Sichuan Province, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China. [3]The Second Hospital of Ningbo, Ningbo 315099, China. [4]Putuo Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China. [5]Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200080, China.

Received: 23 August 2023 Accepted: 28 December 2023
Published online: 09 January 2024

References

1. Ahn J, Barber GN. STING signaling and host defense against microbial infection. Exp Mol Med. 2019;51(12):1–10.
2. Zhang H, You QD, Xu XL. Targeting stimulator of interferon genes (STING): a medicinal chemistry perspective. J Med Chem. 2020;63(8):3785–816.
3. Cohen D, Melamed S, Millman A, Shulman G, Oppenheimer-Shaanan Y, Kacen A, et al. Cyclic GMP-AMP signalling protects bacteria against viral infection. Nature. 2019;574(7780):691–5.
4. Manes NP, Nita-Lazar A. Molecular mechanisms of the toll-like receptor, STING, MAVS, Inflammasome, and Interferon Pathways. mSystems. 2021;6(3):e0033621.
5. Peng Y, Zhuang J, Ying G, Zeng H, Zhou H, Cao Y, et al. Stimulator of IFN genes mediates neuroinflammatory injury by suppressing AMPK signal in experimental subarachnoid hemorrhage. J Neuroinflammation. 2020;17(1):165.
6. Chen Q, Sun L, Chen ZJ. Regulation and function of the cGAS-STING pathway of cytosolic DNA sensing. Nat Immunol. 2016;17(10):1142–9.
7. Zhang X, Bai XC, Chen ZJ. Structures and mechanisms in the cGAS-STING innate immunity pathway. Immunity. 2020;53(1):43–53.
8. 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(1):81.
9. Kwon J, Bakhoum SF. The cytosolic DNA-sensing cGAS-STING pathway in Cancer. Cancer Discov. 2020;10(1):26–39.
10. Samson N, Ablasser A. The cGAS-STING pathway and cancer. Nat Cancer. 2022;3(12):1452–63.
11. Wang Y, Luo J, Alu A, Han X, Wei Y, Wei X. cGAS-STING pathway in cancer biotherapy. Mol Cancer. 2020;19(1):136.
12. Ramanjulu JM, Pesiridis GS, Yang J, Concha N, Singhaus R, Zhang SY, et al. Design of amidobenzimidazole STING receptor agonists with systemic activity. Nature. 2018;564(7736):439–43.
13. Van Herck S, Feng B, Tang L. Delivery of STING agonists for adjuvanting subunit vaccines. Adv Drug Deliv Rev. 2021;179:114020.
14. Wang J, Li P, Yu Y, Fu Y, Jiang H, Lu M, et al. Pulmonary surfactant-biomimetic nanoparticles potentiate heterosubtypic influenza immunity. Science (New York, NY). 2020;367(6480).
15. Luo J, Liu XP, Xiong FF, Gao FX, Yi YL, Zhang M, et al. Enhancing immune response and Heterosubtypic protection ability of inactivated H7N9 vaccine by using STING agonist as a mucosal adjuvant. Front Immunol. 2019;10:2274.
16. Motwani M, Pawaria S, Bernier J, Moses S, Henry K, Fang T, et al. Hierarchy of clinical manifestations in SAVI N153S and V154M mouse models. Proc Natl Acad Sci U S A. 2019;116(16):7941–50.
17. Taguchi T, Mukai K. Innate immunity signalling and membrane trafficking. Curr Opin Cell Biol. 2019;59:1–7.
18. Decout A, Katz JD, Venkatraman S, Ablasser A. The cGAS-STING pathway as a therapeutic target in inflammatory diseases. Nat Rev Immunol. 2021;21(9):548–69.
19. Paul BD, Snyder SH, Bohr VA. Signaling by cGAS-STING in neurodegeneration, Neuroinflammation, and aging. Trends Neurosci. 2021;44(2):83–96.
20. Karmakar M, Katsnelson MA, Dubyak GR, Pearlman E. Neutrophil P2X7 receptors mediate NLRP3 inflammasome-dependent IL-1β secretion in response to ATP. Nat Commun. 2016;7:10555.
21. Paik S, Kim JK, Silwal P, Sasakawa C, Jo EK. An update on the regulatory mechanisms of NLRP3 inflammasome activation. Cell Mol Immunol. 2021;18(5):1141–60.

22. Molyvdas A, Georgopoulou U, Lazaridis N, Hytiroglou P, Dimitriadis A, Foka P, et al. The role of the NLRP3 inflammasome and the activation of IL-1β in the pathogenesis of chronic viral hepatic inflammation. Cytokine. 2018;110:389–96.
23. Karki R, Lee E, Sharma BR, Banoth B, Kanneganti TD. IRF8 regulates gram-negative Bacteria-mediated NLRP3 Inflammasome activation and cell death. J Immunol (Baltimore, Md : 1950). 2020;204(9):2514–22.
24. Wu Y, Ren J, Zhou B, Ding C, Chen J, Wang G, et al. Gene silencing of non-obese diabetic receptor family (NLRP3) protects against the sepsis-induced hyper-bile acidaemia in a rat model. Clin Exp Immunol. 2015;179(2):277–93.
25. Wang Y, Shi P, Chen Q, Huang Z, Zou D, Zhang J, et al. Mitochondrial ROS promote macrophage pyroptosis by inducing GSDMD oxidation. J Mol Cell Biol. 2019;11(12):1069–82.
26. Dick MS, Sborgi L, Rühl S, Hiller S, Broz P. Corrigendum: ASC filament formation serves as a signal amplification mechanism for inflammasomes. Nat Commun. 2017;8:15030.
27. Cheng Q, Pan J, Zhou ZL, Yin F, Xie HY, Chen PP, et al. Caspase-11/4 and gasdermin D-mediated pyroptosis contributes to podocyte injury in mouse diabetic nephropathy. Acta Pharmacol Sin. 2021;42(6):954–63.
28. Miao EA, Leaf IA, Treuting PM, Mao DP, Dors M, Sarkar A, et al. Caspase-1-induced pyroptosis is an innate immune effector mechanism against intracellular bacteria. Nat Immunol. 2010;11(12):1136–42.
29. Jorgensen I, Zhang Y, Krantz BA, Miao EA. Pyroptosis triggers pore-induced intracellular traps (PITs) that capture bacteria and lead to their clearance by efferocytosis. J Exp Med. 2016;213(10):2113–28.
30. Bai B, Yang Y, Wang Q, Li M, Tian C, Liu Y, et al. NLRP3 inflammasome in endothelial dysfunction. Cell Death Dis. 2020;11(9):776.
31. Aachoui Y, Leaf IA, Hagar JA, Fontana MF, Campos CG, Zak DE, et al. Caspase-11 protects against bacteria that escape the vacuole. Science (New York, NY). 2013;339(6122):975–8.
32. Corrales L, Woo SR, Williams JB, McWhirter SM, Dubensky TW Jr, Gajewski TF. Antagonism of the STING pathway via activation of the AIM2 Inflammasome by intracellular DNA. J Immunol (Baltimore, Md : 1950). 2016;196(7):3191–8.
33. Baatarjav C, Komada T, Karasawa T, Yamada N, Sampilvanjil A, Matsumura T, et al. dsDNA-induced AIM2 pyroptosis halts aberrant inflammation during rhabdomyolysis-induced acute kidney injury. Cell Death Differ. 2022;29(12):2487–502.
34. Yan S, Shen H, Lian Q, Jin W, Zhang R, Lin X, et al. Deficiency of the AIM2-ASC signal uncovers the STING-driven Overreactive response of type I IFN and reciprocal depression of protective IFN-γ immunity in mycobacterial infection. J Immunol. 2018;200(3):1016–26.
35. Gray EE, Winship D, Snyder JM, Child SJ, Geballe AP, Stetson DB. The AIM2-like receptors are dispensable for the interferon response to intracellular DNA. Immunity. 2016;45(2):255–66.
36. Jiang H, Swacha P, Gekara NO. Nuclear AIM2-like receptors drive genotoxic tissue injury by inhibiting DNA repair. Adv Sci (Weinh). 2021;8(22):e2102534.
37. Ratsimandresey RA, Dorfleutner A, Stehlik C. An update on PYRIN domain-containing pattern recognition receptors: from immunity to pathology. Front Immunol. 2013;4:440.
38. Brunette RL, Young JM, Whitley DG, Brodsky IE, Malik HS, Stetson DB. Extensive evolutionary and functional diversity among mammalian AIM2-like receptors. J Exp Med. 2012;209(11):1969–83.
39. Kumar V. The trinity of cGAS, TLR9, and ALRs guardians of the cellular galaxy against host-derived self-DNA. Front Immunol. 2020;11:624597.
40. Unterholzner L, Keating SE, Baran M, Horan KA, Jensen SB, Sharma S, et al. IFI16 is an innate immune sensor for intracellular DNA. Nat Immunol. 2010;11(11):997–1004.
41. Schattgen SA, Fitzgerald KA. The PYHIN protein family as mediators of host defenses. Immunol Rev. 2011;243(1):109–18.
42. Nakaya Y, Lilue J, Stavrou S, Moran EA, Ross SR. AIM2-like receptors positively and negatively regulate the interferon response induced by cytosolic DNA. mBio. 2017;8(4).
43. Panchanathan R, Duan X, Shen H, Rathinam VA, Erickson LD, Fitzgerald KA, et al. Aim2 deficiency stimulates the expression of IFN-inducible Ifi202, a lupus susceptibility murine gene within the Nba2 autoimmune susceptibility locus. J Immunol (Baltimore, Md : 1950). 2010;185(12):7385–93.
44. Storek KM, Gertsvolf NA, Ohlson MB, Monack DM. cGAS and Ifi204 cooperate to produce type I IFNs in response to Francisella infection. J Immunol (Baltimore, Md : 1950). 2015;194(7):3236–45.
45. Bühler M, Li D, Li L, Runft S, Waltl I, Pavlou A, et al. IFNAR signaling of neuroectodermal cells is essential for the survival of C57BL/6 mice infected with Theiler's murine encephalomyelitis virus. J Neuroinflammation. 2023;20(1):58.
46. Almine JF, O'Hare CA, Dunphy G, Haga IR, Naik RJ, Atrih A, et al. IFI16 and cGAS cooperate in the activation of STING during DNA sensing in human keratinocytes. Nat Commun. 2017;8:14392.
47. Lee MN, Roy M, Ong SE, Mertins P, Villani AC, Li W, et al. Identification of regulators of the innate immune response to cytosolic DNA and retroviral infection by an integrative approach. Nat Immunol. 2013;14(2):179–85.
48. Cao L, Ji Y, Zeng L, Liu Q, Zhang Z, Guo S, et al. P200 family protein IFI204 negatively regulates type I interferon responses by targeting IRF7 in nucleus. PLoS Pathog. 2019;15(10):e1008079.
49. Chunfa L, Xin S, Qiang L, Sreevatsan S, Yang L, Zhao D, et al. The central role of IFI204 in IFN-β release and autophagy activation during Mycobacterium bovis infection. Front Cell Infect Microbiol. 2017;7:169.
50. Chen W, Yu SX, Zhou FH, Zhang XJ, Gao WY, Li KY, et al. DNA sensor IFI204 contributes to host defense against Staphylococcus aureus infection in mice. Front Immunol. 2019;10:474.
51. Ansari MA, Dutta S, Veettil MV, Dutta D, Iqbal J, Kumar B, et al. Herpesvirus genome recognition induced acetylation of nuclear IFI16 is essential for its cytoplasmic translocation, Inflammasome and IFN-β responses. PLoS Pathog. 2015;11(7):e1005019.
52. Pisano G, Roy A, Ahmed Ansari M, Kumar B, Chikoti L, Chandran B. Interferon-γ-inducible protein 16 (IFI16) is required for the maintenance of Epstein-Barr virus latency. Virol J. 2017;14(1):221.
53. Diner BA, Lum KK, Toettcher JE, Cristea IM. Viral DNA sensors IFI16 and cyclic GMP-AMP synthase possess distinct functions in regulating viral gene expression, immune defenses, and apoptotic responses during herpesvirus infection. mBio. 2016;7(6).
54. Hansen K, Prabakaran T, Laustsen A, Jørgensen SE, Rahbæk SH, Jensen SB, et al. Listeria monocytogenes induces IFNβ expression through an IFI16-, cGAS- and STING-dependent pathway. EMBO J. 2014;33(15):1654–66.
55. Wu T, Gao J, Liu W, Cui J, Yang M, Guo W, et al. NLRP3 protects mice from radiation-induced colon and skin damage via attenuating cGAS-STING signaling. Toxicol Appl Pharmacol. 2021;418:115495.
56. Zheng Y, Liu Q, Wu Y, Ma L, Zhang Z, Liu T, et al. Zika virus elicits inflammation to evade antiviral response by cleaving cGAS via NS1-caspase-1 axis. EMBO J. 2018;37(18).
57. Wang Y, Ning X, Gao P, Wu S, Sha M, Lv M, et al. Inflammasome activation triggers Caspase-1-mediated cleavage of cGAS to regulate responses to DNA virus infection. Immunity. 2017;46(3):393–404.
58. Aglietti RA, Estevez A, Gupta A, Ramirez MG, Liu PS, Kayagaki N, et al. GsdmD p30 elicited by caspase-11 during pyroptosis forms pores in membranes. Proc Natl Acad Sci U S A. 2016;113(28):7858–63.
59. Ding J, Wang K, Liu W, She Y, Sun Q, Shi J, et al. Pore-forming activity and structural autoinhibition of the gasdermin family. Nature. 2016;535(7610):111–6.
60. Liu X, Zhang Z, Ruan J, Pan Y, Magupalli VG, Wu H, et al. Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. Nature. 2016;535(7610):153–8.
61. Sborgi L, Rühl S, Mulvihill E, Pipercevic J, Heilig R, Stahlberg H, et al. GSDMD membrane pore formation constitutes the mechanism of pyroptotic cell death. EMBO J. 2016;35(16):1766–78.
62. Banerjee I, Behl B, Mendonca M, Shrivastava G, Russo AJ, Menoret A, et al. Gasdermin D restrains type I interferon response to cytosolic DNA by disrupting ionic homeostasis. Immunity. 2018;49(3):413-26.e5.
63. Eren E, Berber M, Özören N. NLRC3 protein inhibits inflammation by disrupting NALP3 inflammasome assembly via competition with the adaptor protein ASC for pro-caspase-1 binding. J Biol Chem. 2017;292(30):12691–701.
64. Sandstrom A, Mitchell PS, Goers L, Mu EW, Lesser CF, Vance RE. Functional degradation: a mechanism of NLRP1 inflammasome activation by diverse pathogen enzymes. Science (New York, NY). 2019;364(6435).

65. Chui AJ, Okondo MC, Rao SD, Gai K, Griswold AR, Johnson DC, et al. N-terminal degradation activates the NLRP1B inflammasome. Science (New York, NY). 2019;364(6435):82–5.
66. Zheng C. The emerging roles of NOD-like receptors in antiviral innate immune signaling pathways. Int J Biol Macromol. 2021;169:407–13.
67. Li X, Deng M, Petrucelli AS, Zhu C, Mo J, Zhang L, et al. Viral DNA binding to NLRC3, an inhibitory nucleic acid sensor, unleashes STING, a cyclic dinucleotide receptor that activates type I interferon. Immunity. 2019;50(3):591-9.e6.
68. Zhang L, Mo J, Swanson KV, Wen H, Petrucelli A, Gregory SM, et al. NLRC3, a member of the NLR family of proteins, is a negative regulator of innate immune signaling induced by the DNA sensor STING. Immunity. 2014;40(3):329–41.
69. Guo H, König R, Deng M, Riess M, Mo J, Zhang L, et al. NLRX1 sequesters STING to negatively regulate the interferon response, thereby facilitating the replication of HIV-1 and DNA viruses. Cell Host Microbe. 2016;19(4):515–28.
70. Yang Y, Lang X, Sun S, Gao C, Hu J, Ding S, et al. NLRP2 negatively regulates antiviral immunity by interacting with TBK1. Eur J Immunol. 2018;48(11):1817–25.
71. Cui J, Li Y, Zhu L, Liu D, Songyang Z, Wang HY, et al. NLRP4 negatively regulates type I interferon signaling by targeting the kinase TBK1 for degradation via the ubiquitin ligase DTX4. Nat Immunol. 2012;13(4):387–95.
72. Ellwanger K, Becker E, Kienes I, Sowa A, Postma Y, Cardona Gloria Y, et al. The NLR family pyrin domain-containing 11 protein contributes to the regulation of inflammatory signaling. J Biol Chem. 2018;293(8):2701–10.
73. Abe T, Lee A, Sitharam R, Kesner J, Rabadan R, Shapira SD. Germ-cell-specific Inflammasome component NLRP14 negatively regulates cytosolic nucleic acid sensing to promote fertilization. Immunity. 2017;46(4):621–34.
74. Wang P, Zhu S, Yang L, Cui S, Pan W, Jackson R, et al. Nlrp6 regulates intestinal antiviral innate immunity. Science (New York, NY). 2015;350(6262):826–30.
75. Zhang R, Yang W, Zhu H, Zhai J, Xue M, Zheng C. NLRC4 promotes the cGAS-STING signaling pathway by facilitating CBL-mediated K63-linked polyubiquitination of TBK1. J Med Virol. 2023;95(8):e29013.
76. Sundaram B, Kanneganti TD. Advances in understanding activation and function of the NLRC4 Inflammasome. Int J Mol Sci. 2021;22(3).
77. Kuenzel S, Till A, Winkler M, Häsler R, Lipinski S, Jung S, et al. The nucleotide-binding oligomerization domain-like receptor NLRC5 is involved in IFN-dependent antiviral immune responses. J Immunol (Baltimore, Md : 1950). 2010;184(4):1990–2000.
78. Neerincx A, Lautz K, Menning M, Kremmer E, Zigrino P, Hösel M, et al. A role for the human nucleotide-binding domain, leucine-rich repeat-containing family member NLRC5 in antiviral responses. J Biol Chem. 2010;285(34):26223–32.
79. Gaidt MM, Ebert TS, Chauhan D, Ramshorn K, Pinci F, Zuber S, et al. The DNA Inflammasome in human myeloid cells is initiated by a STING-cell death program upstream of NLRP3. Cell. 2017;171(5):1110-24.e18.
80. Webster SJ, Brode S, Ellis L, Fitzmaurice TJ, Elder MJ, Gekara NO, et al. Detection of a microbial metabolite by STING regulates inflammasome activation in response to chlamydia trachomatis infection. PLoS Pathog. 2017;13(6):e1006383.
81. Zhong W, Rao Z, Rao J, Han G, Wang P, Jiang T, et al. Aging aggravated liver ischemia and reperfusion injury by promoting STING-mediated NLRP3 activation in macrophages. Aging Cell. 2020;19(8):e13186.
82. Li N, Zhou H, Wu H, Wu Q, Duan M, Deng W, et al. STING-IRF3 contributes to lipopolysaccharide-induced cardiac dysfunction, inflammation, apoptosis and pyroptosis by activating NLRP3. Redox Biol. 2019;24:101215.
83. Zhang H, Chen Z, Zhou J, Gu J, Wu H, Jiang Y, et al. NAT10 regulates neutrophil pyroptosis in sepsis via acetylating ULK1 RNA and activating STING pathway. Commun Biol. 2022;5(1):916.
84. McLemore AF, Hou HA, Meyer BS, Lam NB, Ward GA, Aldrich AL, et al. Somatic gene mutations expose cytoplasmic DNA to co-opt the cGAS/STING/NLRP3 axis in myelodysplastic syndromes. JCI Insight. 2022;7(15).
85. Aits S, Jäättelä M. Lysosomal cell death at a glance. J Cell Sci. 2013;126(Pt 9):1905–12.
86. Wang W, Hu D, Wu C, Feng Y, Li A, Liu W, et al. STING promotes NLRP3 localization in ER and facilitates NLRP3 deubiquitination to activate the inflammasome upon HSV-1 infection. PLoS Pathog. 2020;16(3):e1008335.
87. Xiao Y, Zhao C, Tai Y, Li B, Lan T, Lai E, et al. STING mediates hepatocyte pyroptosis in liver fibrosis by epigenetically activating the NLRP3 inflammasome. Redox Biol. 2023;62:102691.
88. Cridland JA, Curley EZ, Wykes MN, Schroder K, Sweet MJ, Roberts TL, et al. The mammalian PYHIN gene family: phylogeny, evolution and expression. BMC Evol Biol. 2012;12:140.
89. Man SM, Karki R, Kanneganti TD. AIM2 inflammasome in infection, cancer, and autoimmunity: role in DNA sensing, inflammation, and innate immunity. Eur J Immunol. 2016;46(2):269–80.
90. Liu F, Niu Q, Fan X, Liu C, Zhang J, Wei Z, et al. Priming and activation of Inflammasome by canarypox virus vector ALVAC via the cGAS/IFI16-STING-type I IFN pathway and AIM2 sensor. J Immunol. 2017;199(9):3293–305.
91. Song X, Ma F, Herrup K. Accumulation of cytoplasmic DNA due to ATM deficiency activates the microglial viral response system with neurotoxic consequences. J Neurosci. 2019;39(32):6378–94.
92. Man SM, Karki R, Malireddi RK, Neale G, Vogel P, Yamamoto M, et al. The transcription factor IRF1 and guanylate-binding proteins target activation of the AIM2 inflammasome by Francisella infection. Nat Immunol. 2015;16(5):467–75.
93. Costa Franco MM, Marim F, Guimarães ES, Assis NRG, Cerqueira DM, Alves-Silva J, et al. Brucella abortus triggers a cGAS-independent STING pathway to induce host protection that involves guanylate-binding proteins and Inflammasome activation. J Immunol. 2018;200(2):607–22.
94. Brault M, Olsen TM, Martinez J, Stetson DB, Oberst A. Intracellular nucleic acid sensing triggers necroptosis through synergistic type I IFN and TNF signaling. J Immunol (Baltimore, Md : 1950). 2018;200(8):2748–56.
95. Chen D, Tong J, Yang L, Wei L, Stolz DB, Yu J, et al. PUMA amplifies necroptosis signaling by activating cytosolic DNA sensors. Proc Natl Acad Sci U S A. 2018;115(15):3930–5.
96. Cui Y, Zhao D, Sreevatsan S, Liu C, Yang W, Song Z, et al. Mycobacterium bovis induces endoplasmic reticulum stress mediated-apoptosis by activating IRF3 in a murine macrophage cell line. Front Cell Infect Microbiol. 2016;6:182.
97. Petrasek J, Iracheta-Vellve A, Csak T, Satishchandran A, Kodys K, Kurt-Jones EA, et al. STING-IRF3 pathway links endoplasmic reticulum stress with hepatocyte apoptosis in early alcoholic liver disease. Proc Natl Acad Sci U S A. 2013;110(41):16544–9.
98. Wu J, Chen YJ, Dobbs N, Sakai T, Liou J, Miner JJ, et al. STING-mediated disruption of calcium homeostasis chronically activates ER stress and primes T cell death. J Exp Med. 2019;216(4):867–83.
99. Gurung P, Lukens JR, Kanneganti TD. Mitochondria: diversity in the regulation of the NLRP3 inflammasome. Trends Mol Med. 2015;21(3):193–201.
100. 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(7548):553–7.
101. Hopfner KP, Hornung V. Molecular mechanisms and cellular functions of cGAS-STING signalling. Nat Rev Mol Cell Biol. 2020;21(9):501–21.
102. Lawrence G, Holley CL, Schroder K. Come on mtDNA, light my fire. Immunity. 2022;55(8):1331–3.
103. Zhong Z, Umemura A, Sanchez-Lopez E, Liang S, Shalapour S, Wong J, et al. NF-κB restricts Inflammasome activation via elimination of damaged mitochondria. Cell. 2016;164(5):896–910.
104. Xian H, Watari K, Sanchez-Lopez E, Offenberger J, Onyuru J, Sampath H, et al. Oxidized DNA fragments exit mitochondria via mPTP- and VDAC-dependent channels to activate NLRP3 inflammasome and interferon signaling. Immunity. 2022;55(8):1370-85.e8.
105. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev. 2004;84(1):277–359.
106. Fenzl A, Kiefer FW. Brown adipose tissue and thermogenesis. Horm Mol Biol Clin Investig. 2014;19(1):25–37.
107. Montanari T, Pošćić N, Colitti M. Factors involved in white-to-brown adipose tissue conversion and in thermogenesis: a review. Obes Rev. 2017;18(5):495–513.
108. Lee JH, Park A, Oh KJ, Lee SC, Kim WK, Bae KH. The role of adipose tissue mitochondria: regulation of mitochondrial function for the treatment of metabolic diseases. Int J Mol Sci. 2019;20(19).

109. Rosina M, Ceci V, Turchi R, Chuan L, Borcherding N, Sciarretta F, et al. Ejection of damaged mitochondria and their removal by macrophages ensure efficient thermogenesis in brown adipose tissue. Cell Metab. 2022;34(4):533-48.e12.
110. Wang G, Meyer JG, Cai W, Softic S, Li ME, Verdin E, et al. Regulation of UCP1 and mitochondrial metabolism in Brown adipose tissue by reversible Succinylation. Mol Cell. 2019;74(4):844-57.e7.
111. Huang Y, Zhou JH, Zhang H, Canfran-Duque A, Singh AK, Perry RJ, et al. Brown adipose TRX2 deficiency activates mtDNA-NLRP3 to impair thermogenesis and protect against diet-induced insulin resistance. J Clin Invest. 2022;132(9).
112. Liu Z, Wang M, Wang X, Bu Q, Wang Q, Su W, et al. XBP1 deficiency promotes hepatocyte pyroptosis by impairing mitophagy to activate mtDNA-cGAS-STING signaling in macrophages during acute liver injury. Redox Biol. 2022;52:102305.
113. Wassermann R, Gulen MF, Sala C, Perin SG, Lou Y, Rybniker J, et al. Mycobacterium tuberculosis differentially activates cGAS- and Inflammasome-dependent intracellular immune responses through ESX-1. Cell Host Microbe. 2015;17(6):799–810.
114. Wiens KE, Ernst JD. The mechanism for type I interferon induction by mycobacterium tuberculosis is bacterial strain-dependent. PLoS Pathog. 2016;12(8):e1005809.
115. Kim BR, Kim BJ, Kook YH, Kim BJ. Mycobacterium abscessus infection leads to enhanced production of type 1 interferon and NLRP3 inflammasome activation in murine macrophages via mitochondrial oxidative stress. PLoS Pathog. 2020;16(3):e1008294.
116. Guarda G, Braun M, Staehli F, Tardivel A, Mattmann C, Förster I, et al. Type I interferon inhibits interleukin-1 production and inflammasome activation. Immunity. 2011;34(2):213–23.
117. Mayer-Barber KD, Yan B. Clash of the cytokine titans: counter-regulation of interleukin-1 and type I interferon-mediated inflammatory responses. Cell Mol Immunol. 2017;14(1):22–35.
118. Kopitar-Jerala N. The role of interferons in inflammation and Inflammasome activation. Front Immunol. 2017;8:873.
119. Seo GJ, Kim C, Shin WJ, Sklan EH, Eoh H, Jung JU. TRIM56-mediated monoubiquitination of cGAS for cytosolic DNA sensing. Nat Commun. 2018;9(1):613.
120. Wang C, Guan Y, Lv M, Zhang R, Guo Z, Wei X, et al. Manganese increases the sensitivity of the cGAS-STING pathway for double-stranded DNA and is required for the host defense against DNA viruses. Immunity. 2018;48(4):675-87.e7.
121. Zi J, Han Q, Gu S, McGrath M, Kane S, Song C, et al. Targeting NAT10 induces apoptosis associated with enhancing endoplasmic reticulum stress in acute myeloid leukemia cells. Front Oncol. 2020;10:598107.
122. Liu X, Cai S, Zhang C, Liu Z, Luo J, Xing B, et al. Deacetylation of NAT10 by Sirt1 promotes the transition from rRNA biogenesis to autophagy upon energy stress. Nucleic Acids Res. 2018;46(18):9601–16.
123. Denning NL, Aziz M, Gurien SD, Wang P. DAMPs and NETs in Sepsis. Front Immunol. 2019;10:2536.
124. Qiao H, Chiu Y, Liang X, Xia S, Ayrapetyan M, Liu S, et al. Microglia innate immune response contributes to the antiviral defense and blood-CSF barrier function in human choroid plexus organoids during HSV-1 infection. J Med Virol. 2023;95(2):e28472.
125. Konno H, Konno K, Barber GN. Cyclic dinucleotides trigger ULK1 (ATG1) phosphorylation of STING to prevent sustained innate immune signaling. Cell. 2013;155(3):688–98.
126. Kimura T, Jain A, Choi SW, Mandell MA, Schroder K, Johansen T, et al. TRIM-mediated precision autophagy targets cytoplasmic regulators of innate immunity. J Cell Biol. 2015;210(6):973–89.
127. Swanson KV, Junkins RD, Kurkjian CJ, Holley-Guthrie E, Pendse AA, El Morabiti R, et al. A noncanonical function of cGAMP in inflammasome priming and activation. J Exp Med. 2017;214(12):3611–26.
128. Denk D, Greten FR. Inflammation: the incubator of the tumor microenvironment. Trends Cancer. 2022;8(11):901–14.
129. Afify SM, Hassan G, Seno A, Seno M. Cancer-inducing niche: the force of chronic inflammation. Br J Cancer. 2022;127(2):193–201.
130. Greten FR, Grivennikov SI. Inflammation and Cancer: triggers, mechanisms, and consequences. Immunity. 2019;51(1):27–41.
131. Chen Z, Zhou L, Liu L, Hou Y, Xiong M, Yang Y, et al. Single-cell RNA sequencing highlights the role of inflammatory cancer-associated fibroblasts in bladder urothelial carcinoma. Nat Commun. 2020;11(1):5077.
132. Fleming TP, Watkins AJ, Velazquez MA, Mathers JC, Prentice AM, Stephenson J, et al. Origins of lifetime health around the time of conception: causes and consequences. Lancet. 2018;391(10132):1842–52.
133. Renz H, Holt PG, Inouye M, Logan AC, Prescott SL, Sly PD. An exposome perspective: early-life events and immune development in a changing world. J Allergy Clin Immunol. 2017;140(1):24–40.
134. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25(12):1822–32.
135. 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(4):e11002.
136. Du Y, Hu Z, Luo Y, Wang HY, Yu X, Wang RF. Function and regulation of cGAS-STING signaling in infectious diseases. Front Immunol. 2023;14:1130423.
137. Zhang D, Liu Y, Zhu Y, Zhang Q, Guan H, Liu S, et al. A non-canonical cGAS-STING-PERK pathway facilitates the translational program critical for senescence and organ fibrosis. Nat Cell Biol. 2022;24(5):766–82.
138. 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(7973):374–80.
139. Yan M, Li Y, Luo Q, Zeng W, Shao X, Li L, et al. Mitochondrial damage and activation of the cytosolic DNA sensor cGAS-STING pathway lead to cardiac pyroptosis and hypertrophy in diabetic cardiomyopathy mice. Cell Death Discov. 2022;8(1):258.
140. Han J, Dai S, Zhong L, Shi X, Fan X, Zhong X, et al. GSDMD (Gasdermin D) Mediates Pathological Cardiac Hypertrophy and Generates a Feed-Forward Amplification Cascade via Mitochondria-STING (Stimulator of Interferon Genes) Axis. Hypertension (Dallas, Tex : 1979). 2022;79(11):2505–18.
141. Lv N, Zhao Y, Liu X, Ye L, Liang Z, Kang Y, et al. Dysfunctional telomeres through mitostress-induced cGAS/STING activation to aggravate immune senescence and viral pneumonia. Aging Cell. 2022;21(4):e13594.
142. Ning L, Wei W, Wenyang J, Rui X, Qing G. Cytosolic DNA-STING-NLRP3 axis is involved in murine acute lung injury induced by lipopolysaccharide. Clin Transl Med. 2020;10(7):e228.
143. Long G, Gong R, Wang Q, Zhang D, Huang C. Role of released mitochondrial DNA in acute lung injury. Front Immunol. 2022;13:973089.
144. Messaoud-Nacer Y, Culerier E, Rose S, Maillet I, Rouxel N, Briault S, et al. STING agonist diABZI induces PANoptosis and DNA mediated acute respiratory distress syndrome (ARDS). Cell Death Dis. 2022;13(3):269.
145. Zhang Y, Li Z, Hong W, Hsu S, Wang B, Zeng Z, et al. STING-dependent sensing of self-DNA driving pyroptosis contributes to radiation-induced lung injury. Int J Radiat Oncol Biol Phys. 2023;117.
146. Xu D, Tian Y, Xia Q, Ke B. The cGAS-STING pathway: novel perspectives in liver diseases. Front Immunol. 2021;12:682736.
147. Wang Z, Chen N, Li Z, Xu G, Zhan X, Tang J, et al. The cytosolic DNA-sensing cGAS-STING pathway in liver diseases. Front Cell Dev Biol. 2021;9:717610.
148. de Carvalho RM, Szabo G. Role of the Inflammasome in liver disease. Annu Rev Pathol. 2022;17:345–65.
149. Szabo G, Csak T. Inflammasomes in liver diseases. J Hepatol. 2012;57(3):642–54.
150. Yu Y, Liu Y, An W, Song J, Zhang Y, Zhao X. STING-mediated inflammation in Kupffer cells contributes to progression of nonalcoholic steatohepatitis. J Clin Invest. 2019;129(2):546–55.
151. Luo X, Li H, Ma L, Zhou J, Guo X, Woo SL, et al. Expression of STING is increased in liver tissues from patients with NAFLD and promotes macrophage-mediated hepatic inflammation and fibrosis in mice. Gastroenterology. 2018;155(6):1971-84.e4.
152. Xian H, Liu Y, Rundberg Nilsson A, Gatchalian R, Crother TR, Tourtellotte WG, et al. Metformin inhibition of mitochondrial ATP and DNA synthesis abrogates NLRP3 inflammasome activation and pulmonary inflammation. Immunity. 2021;54(7):1463-77.e11.
153. Iracheta-Vellve A, Petrasek J, Gyongyosi B, Satishchandran A, Lowe P, Kodys K, et al. Endoplasmic reticulum stress-induced hepatocellular death pathways mediate liver injury and fibrosis via stimulator of interferon genes. J Biol Chem. 2016;291(52):26794–805.

154. Yong H, Wang S, Song F. Activation of cGAS/STING pathway upon TDP-43-mediated mitochondrial injury may be involved in the pathogenesis of liver fibrosis. Liver Int : Off J Int Assoc Study Liver. 2021;41(8):1969–71.
155. Li Y, He M, Wang Z, Duan Z, Guo Z, Wang Z, et al. STING signaling activation inhibits HBV replication and attenuates the severity of liver injury and HBV-induced fibrosis. Cell Mol Immunol. 2022;19(1):92–107.
156. Gautheron J, Gores GJ, Rodrigues CMP. Lytic cell death in metabolic liver disease. J Hepatol. 2020;73(2):394–408.
157. Wu J, Lin S, Wan B, Velani B, Zhu Y. Pyroptosis in liver disease: new insights into disease mechanisms. Aging Dis. 2019;10(5):1094–108.
158. Wree A, Eguchi A, McGeough MD, Pena CA, Johnson CD, Canbay A, et al. NLRP3 inflammasome activation results in hepatocyte pyroptosis, liver inflammation, and fibrosis in mice. Hepatology (Baltimore, Md). 2014;59(3):898–910.
159. Gaul S, Leszczynska A, Alegre F, Kaufmann B, Johnson CD, Adams LA, et al. Hepatocyte pyroptosis and release of inflammasome particles induce stellate cell activation and liver fibrosis. J Hepatol. 2021;74(1):156–67.
160. Wu XY, Chen YJ, Liu CA, Gong JH, Xu XS. STING induces liver ischemia-reperfusion injury by promoting calcium-dependent caspase 1-GSDMD processing in macrophages. Oxidative Med Cell Longev. 2022;2022:8123157.
161. Li HY, Chien Y, Chen YJ, Chen SF, Chang YL, Chiang CH, et al. Reprogramming induced pluripotent stem cells in the absence of c-Myc for differentiation into hepatocyte-like cells. Biomaterials. 2011;32(26):5994–6005.
162. Dat NQ, Thuy LTT, Hieu VN, Hai H, Hoang DV, Thi Thanh Hai N, et al. Hexa Histidine-Tagged Recombinant Human Cytoglobin Deactivates Hepatic Stellate Cells and Inhibits Liver Fibrosis by Scavenging Reactive Oxygen Species. Hepatology (Baltimore, Md). 2021;73(6):2527–45.
163. Evavold CL, Hafner-Bratkovič I, Devant P, D'Andrea JM, Ngwa EM, Boršić E, et al. Control of gasdermin D oligomerization and pyroptosis by the Ragulator-rag-mTORC1 pathway. Cell. 2021;184(17):4495-511.e19.
164. Jia D, Gong L, Li Y, Cao S, Zhao W, Hao L, et al. {BiW(8) O(30) } exerts antitumor effect by triggering pyroptosis and upregulating reactive oxygen species. Angewandte Chemie (International ed in English). 2021;60(39):21449–56.
165. Lameire NH, Bagga A, Cruz D, De Maeseneer J, Endre Z, Kellum JA, et al. Acute kidney injury: an increasing global concern. Lancet (London, England). 2013;382(9887):170–9.
166. Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM, et al. Acute kidney disease and renal recovery: consensus report of the acute disease quality initiative (ADQI) 16 workgroup. Nat Rev Nephrol. 2017;13(4):241–57.
167. Tsuji N, Tsuji T, Ohashi N, Kato A, Fujigaki Y, Yasuda H. Role of mitochondrial DNA in septic AKI via toll-like receptor 9. J Am Soc Nephrol : JASN. 2016;27(7):2009–20.
168. Maekawa H, Inoue T, Ouchi H, Jao TM, Inoue R, Nishi H, et al. Mitochondrial damage causes inflammation via cGAS-STING signaling in acute kidney injury. Cell Rep. 2019;29(5):1261-73.e6.
169. Homolová J, Janovičová Ľ, Konečná B, Vlková B, Celec P, Tóthová Ľ, et al. Plasma concentrations of extracellular DNA in acute kidney injury. Diagnostics (Basel, Switzerland). 2020;10(3).
170. Inoue T, Abe C, Sung SS, Moscalu S, Jankowski J, Huang L, et al. Vagus nerve stimulation mediates protection from kidney ischemia-reperfusion injury through α7nAChR+ splenocytes. J Clin Invest. 2016;126(5):1939–52.
171. Kojima I, Tanaka T, Inagi R, Kato H, Yamashita T, Sakiyama A, et al. Protective role of hypoxia-inducible factor-2alpha against ischemic damage and oxidative stress in the kidney. J Am Soc Nephrol : JASN. 2007;18(4):1218–26.
172. Correa-Costa M, Braga TT, Semedo P, Hayashida CY, Bechara LR, Elias RM, et al. Pivotal role of toll-like receptors 2 and 4, its adaptor molecule MyD88, and inflammasome complex in experimental tubule-interstitial nephritis. PLoS One. 2011;6(12):e29004.
173. Vilaysane A, Chun J, Seamone ME, Wang W, Chin R, Hirota S, et al. The NLRP3 inflammasome promotes renal inflammation and contributes to CKD. J Am Soc Nephrol : JASN. 2010;21(10):1732–44.
174. Gong W, Mao S, Yu J, Song J, Jia Z, Huang S, et al. NLRP3 deletion protects against renal fibrosis and attenuates mitochondrial abnormality in mouse with 5/6 nephrectomy. Am J Physiol Renal Physiol. 2016;310(10):F1081–8.
175. Wu J, Raman A, Coffey NJ, Sheng X, Wahba J, Seasock MJ, et al. The key role of NLRP3 and STING in APOL1-associated podocytopathy. J Clin Invest. 2021;131(20).
176. Eldahshan W, Fagan SC, Ergul A. Inflammation within the neurovascular unit: focus on microglia for stroke injury and recovery. Pharmacol Res. 2019;147:104349.
177. Han B, Jiang W, Cui P, Zheng K, Dang C, Wang J, et al. Microglial PGC-1α protects against ischemic brain injury by suppressing neuroinflammation. Genome Med. 2021;13(1):47.
178. Xu P, Hong Y, Xie Y, Yuan K, Li J, Sun R, et al. TREM-1 exacerbates Neuroinflammatory injury via NLRP3 Inflammasome-mediated Pyroptosis in experimental subarachnoid hemorrhage. Transl Stroke Res. 2021;12(4):643–59.
179. Ran Y, Su W, Gao F, Ding Z, Yang S, Ye L, et al. Curcumin ameliorates white matter injury after ischemic stroke by inhibiting microglia/macrophage Pyroptosis through NF-κB suppression and NLRP3 Inflammasome inhibition. Oxidative Med Cell Longev. 2021;2021:1552127.
180. Xu P, Zhang X, Liu Q, Xie Y, Shi X, Chen J, et al. Microglial TREM-1 receptor mediates neuroinflammatory injury via interaction with SYK in experimental ischemic stroke. Cell Death Dis. 2019;10(8):555.
181. Xu S, Wang J, Zhong J, Shao M, Jiang J, Song J, et al. CD73 alleviates GSDMD-mediated microglia pyroptosis in spinal cord injury through PI3K/AKT/Foxo1 signaling. Clin Transl Med. 2021;11(1):e269.
182. 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(1):137.
183. Liu J, Zhang X, Wang H. The cGAS-STING-mediated NLRP3 inflammasome is involved in the neurotoxicity induced by manganese exposure. Biomed Pharmacother = Biomed Pharmacother. 2022;154:113680.
184. 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(5):914–27.
185. Sarkar S, Rokad D, Malovic E, Luo J, Harischandra DS, Jin H, et al. Manganese activates NLRP3 inflammasome signaling and propagates exosomal release of ASC in microglial cells. Sci Signal. 2019;12(563).
186. Nuber UA, Kriaucionis S, Roloff TC, Guy J, Selfridge J, Steinhoff C, et al. Up-regulation of glucocorticoid-regulated genes in a mouse model of Rett syndrome. Hum Mol Genet. 2005;14(15):2247–56.
187. Lang F, Strutz-Seebohm N, Seebohm G, Lang UE. Significance of SGK1 in the regulation of neuronal function. J Physiol. 2010;588(Pt 18):3349–54.
188. Zhang Z, Li XG, Wang ZH, Song M, Yu SP, Kang SS, et al. δ-secretase-cleaved tau stimulates Aβ production via upregulating STAT1-BACE1 signaling in Alzheimer's disease. Mol Psychiatry. 2021;26(2):586–603.
189. Wang L, Li B, Quan MY, Li L, Chen Y, Tan GJ, et al. Mechanism of oxidative stress p38MAPK-SGK1 signaling axis in experimental autoimmune encephalomyelitis (EAE). Oncotarget. 2017;8(26):42808–16.
190. Schoenebeck B, Bader V, Zhu XR, Schmitz B, Lübbert H, Stichel CC. Sgk1, a cell survival response in neurodegenerative diseases. Mol Cell Neurosci. 2005;30(2):249–64.
191. Peng HY, Chen GD, Lai CY, Hsieh MC, Lin TB. Spinal serum-inducible and glucocorticoid-inducible kinase 1 mediates neuropathic pain via kalirin and downstream PSD-95-dependent NR2B phosphorylation in rats. J Neurosci. 2013;33(12):5227–40.
192. 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(4):e13076.
193. 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(37).
194. Zhang LM, Xin Y, Wu ZY, Song RX, Miao HT, Zheng WC, et al. STING mediates neuroinflammatory response by activating NLRP3-related pyroptosis in severe traumatic brain injury. J Neurochem. 2022;162(5):444–62.

195. Wobma H, Shin DS, Chou J, Dedeoд÷lu F. Dysregulation of the cGAS-STING pathway in monogenic autoinflammation and lupus. Front Immunol. 2022;13:905109.
196. Basiorka AA, McGraw KL, Eksioglu EA, Chen X, Johnson J, Zhang L, et al. The NLRP3 inflammasome functions as a driver of the myelodysplastic syndrome phenotype. Blood. 2016;128(25):2960–75.
197. 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(2):129–42.
198. Barrera MJ, Aguilera S, Castro I, Carvajal P, Jara D, Molina C, et al. Dysfunctional mitochondria as critical players in the inflammation of autoimmune diseases: potential role in Sjögren's syndrome. Autoimmun Rev. 2021;20(8):102867.
199. Lin B, Goldbach-Mansky R. Pathogenic insights from genetic causes of autoinflammatory inflammasomopathies and interferonopathies. J Allergy Clin Immunol. 2022;149(3):819–32.
200. Inokuchi S, Mitoma H, Kawano S, Ayano M, Kimoto Y, Akahoshi M, et al. Activation of caspase-1 is mediated by stimulation of interferon genes and NLR family pyrin domain containing 3 in monocytes of active systemic lupus erythematosus. Clin Exp Rheumatol. 2022;40(3):522–31.
201. Kogan AA, Topper MJ, Dellomo AJ, Stojanovic L, McLaughlin LJ, Creed TM, et al. Activating STING1-dependent immune signaling in TP53 mutant and wild-type acute myeloid leukemia. Proc Natl Acad Sci U S A. 2022;119(27):e2123227119.
202. Gu L, Sun Y, Wu T, Chen G, Tang X, Zhao L, et al. A novel mechanism for macrophage pyroptosis in rheumatoid arthritis induced by pol β deficiency. Cell Death Dis. 2022;13(7):583.
203. Hou J, Karin M, Sun B. Targeting cancer-promoting inflammation - have anti-inflammatory therapies come of age? Nat Rev Clin Oncol. 2021;18(5):261–79.
204. Li A, Yi M, Qin S, Song Y, Chu Q, Wu K. Activating cGAS-STING pathway for the optimal effect of cancer immunotherapy. J Hematol Oncol. 2019;12(1):35.
205. Sun Y, Hu H, Liu Z, Xu J, Gao Y, Zhan X, et al. Macrophage STING signaling promotes NK cell to suppress colorectal cancer liver metastasis via 4-1BBL/4-1BB co-stimulation. J Immunother Cancer. 2023;11(3).
206. Dupaul-Chicoine J, Arabzadeh A, Dagenais M, Douglas T, Champagne C, Morizot A, et al. The Nlrp3 Inflammasome suppresses colorectal Cancer metastatic growth in the liver by promoting natural killer cell Tumoricidal activity. Immunity. 2015;43(4):751–63.
207. Chen Q, Boire A, Jin X, Valiente M, Er EE, Lopez-Soto A, et al. Carcinoma-astrocyte gap junctions promote brain metastasis by cGAMP transfer. Nature. 2016;533(7604):493–8.
208. Sefik E, Qu R, Junqueira C, Kaffe E, Mirza H, Zhao J, et al. Inflammasome activation in infected macrophages drives COVID-19 pathology. Nature. 2022;606(7914):585–93.
209. Zhao N, Di B, Xu LL. The NLRP3 inflammasome and COVID-19: activation, pathogenesis and therapeutic strategies. Cytokine Growth Factor Rev. 2021;61:2–15.
210. Vora SM, Lieberman J, Wu H. Inflammasome activation at the crux of severe COVID-19. Nat Rev Immunol. 2021;21(11):694–703.
211. Potere N, Del Buono MG, Caricchio R, Cremer PC, Vecchie A, Porreca E, et al. Interleukin-1 and the NLRP3 inflammasome in COVID-19: Pathogenetic and therapeutic implications. EBioMedicine. 2022;85:104299.
212. Domizio JD, Gulen MF, Saidoune F, Thacker VV, Yatim A, Sharma K, et al. The cGAS-STING pathway drives type I IFN immunopathology in COVID-19. Nature. 2022;603(7899):145–51.
213. Xiao R, Zhang A. Involvement of the STING signaling in COVID-19. Front Immunol. 2022;13:1006395.
214. Li M, Ferretti M, Ying B, Descamps H, Lee E, Dittmar M, et al. Pharmacological activation of STING blocks SARS-CoV-2 infection. Sci Immunol. 2021;6(59).
215. Zhang Y, Yan J, Hou X, Wang C, Kang DD, Xue Y, et al. STING agonist-derived LNP-mRNA vaccine enhances protective immunity against SARS-CoV-2. Nano Lett. 2023;23(7):2593–600.
216. Wu Y, Zhang M, Yuan C, Ma Z, Li W, Zhang Y, et al. Progress of cGAS-STING signaling in response to SARS-CoV-2 infection. Front Immunol. 2022;13:1010911.
217. Wu YT, Xu WT, Zheng L, Wang S, Wei J, Liu MY, et al. 4-octyl itaconate ameliorates alveolar macrophage pyroptosis against ARDS via rescuing mitochondrial dysfunction and suppressing the cGAS/STING pathway. Int Immunopharmacol. 2023;118:110104.
218. Tian Y, Bao Z, Ji Y, Mei X, Yang H. Epigallocatechin-3-Gallate protects H(2)O(2)-induced nucleus pulposus cell apoptosis and inflammation by inhibiting cGAS/Sting/NLRP3 activation. Drug Des Devel Ther. 2020;14:2113–22.
219. Meng G, Zhao S, Xie L, Han Y, Ji Y. Protein S-sulfhydration by hydrogen sulfide in cardiovascular system. Br J Pharmacol. 2018;175(8):1146–56.
220. Yuan S, Shen X, Kevil CG. Beyond a Gasotransmitter: hydrogen sulfide and polysulfide in cardiovascular health and immune response. Antioxid Redox Signal. 2017;27(10):634–53.
221. Mani S, Li H, Untereiner A, Wu L, Yang G, Austin RC, et al. Decreased endogenous production of hydrogen sulfide accelerates atherosclerosis. Circulation. 2013;127(25):2523–34.
222. Yang G, Wu L, Jiang B, Yang W, Qi J, Cao K, et al. H2S as a physiologic vasorelaxant: hypertension in mice with deletion of cystathionine gamma-lyase. Science (New York, NY). 2008;322(5901):587–90.
223. LaPenna KB, Polhemus DJ, Doiron JE, Hidalgo HA, Li Z, Lefer DJ. Hydrogen sulfide as a potential therapy for heart failure-past, present, and future. Antioxidants (Basel, Switzerland). 2021;10(3).
224. Bai L, Dai J, Xia Y, He K, Xue H, Guo Q, et al. Hydrogen sulfide ameliorated high choline-induced cardiac dysfunction by inhibiting cGAS-STING-NLRP3 Inflammasome pathway. Oxidative Med Cell Longev. 2022;2022:1392896.
225. Shen P, Han L, Chen G, Cheng Z, Liu Q. Emodin attenuates acetaminophen-induced hepatotoxicity via the cGAS-STING pathway. Inflammation. 2022;45(1):74–87.
226. Zhang C, Song Y, Chen L, Chen P, Yuan M, Meng Y, et al. Urolithin a attenuates Hyperuricemic nephropathy in fructose-fed mice by impairing STING-NLRP3 Axis-mediated inflammatory response via restoration of Parkin-dependent Mitophagy. Front Pharmacol. 2022;13:907209.
227. Ma Z, Ni G, Damania B. Innate sensing of DNA virus genomes. Annu Rev Virol. 2018;5(1):341–62.
228. Su T, Zhang Y, Valerie K, Wang XY, Lin S, Zhu G. STING activation in cancer immunotherapy. Theranostics. 2019;9(25):7759–71.
229. Ming SL, Zeng L, Guo YK, Zhang S, Li GL, Ma YX, et al. The human-specific STING agonist G10 activates type I interferon and the NLRP3 Inflammasome in porcine cells. Front Immunol. 2020;11:575818.
230. Gröschel MI, Sayes F, Shin SJ, Frigui W, Pawlik A, Orgeur M, et al. Recombinant BCG expressing ESX-1 of Mycobacterium marinum combines low virulence with cytosolic immune signaling and improved TB protection. Cell Rep. 2017;18(11):2752–65.
231. Ma C, Ma X, Jiang B, Pan H, Liao X, Zhang L, et al. A novel inactivated whole-cell Pseudomonas aeruginosa vaccine that acts through the cGAS-STING pathway. Signal Transduct Target Ther. 2021;6(1):353.
232. Miura N, Shaheen SM, Akita H, Nakamura T, Harashima H. A KALA-modified lipid nanoparticle containing CpG-free plasmid DNA as a potential DNA vaccine carrier for antigen presentation and as an immune-stimulative adjuvant. Nucleic Acids Res. 2015;43(3):1317–31.
233. Xu X, Fan H, Yang Y, Yao S, Yu W, Guo Z, et al. Virus-Like Particle-Induced cGAS-STING Activation and AIM2 Inflammasome-Mediated Pyroptosis for Robust Cancer Immunotherapy. Angewandte Chemie (International ed in English). 2023;135:e202303010.
234. Chen D, Le SB, Hutchinson TE, Calinescu AA, Sebastian M, Jin D, et al. Tumor treating fields dually activate STING and AIM2 inflammasomes to induce adjuvant immunity in glioblastoma. J Clin Invest. 2022;132(8).
235. Ling YY, Xia XY, Hao L, Wang WJ, Zhang H, Liu LY, et al. Simultaneous Photoactivation of cGAS-STING pathway and Pyroptosis by platinum(II) Triphenylamine complexes for Cancer immunotherapy. Angewandte Chemie (International ed in English). 2022;61(43):e202210988.
236. Liu YG, Chen JK, Zhang ZT, Ma XJ, Chen YC, Du XM, et al. NLRP3 inflammasome activation mediates radiation-induced pyroptosis in bone marrow-derived macrophages. Cell Death Dis. 2017;8(2):e2579.
237. Kabiljo J, Harpain F, Carotta S, Bergmann M. Radiotherapy as a backbone for novel concepts in Cancer immunotherapy. Cancers. 2019;12(1).
238. Barber GN. STING: infection, inflammation and cancer. Nat Rev Immunol. 2015;15(12):760–70.

Publisher's Note