The cGAS-STING Pathway in Hematopoiesis and Its Physiopathological Significance

Weinian Liao, Changhong Du and Junping Wang*

State Key Laboratory of Trauma, Burns and Combined Injury, Institute of Combined Injury, Chongqing Engineering Research Center for Nanomedicine, College of Preventive Medicine, Army Medical University (Third Military Medical University), Chongqing, China

Cytosolic DNA sensing is a fundamental mechanism by which organisms handle various stresses, including infection and genotoxicity. The hematopoietic system is sensitive to stresses, and hematopoietic changes are often rapid and the first response to stresses. Based on the transcriptome database, cytosolic DNA sensing pathways are widely expressed in the hematopoietic system, and components of these pathways may be expressed at even higher levels in hematopoietic stem and progenitor cells (HSPCs) than in their certain progeny immune cells. Recent studies have described a previously unrecognized role for cytosolic DNA sensing pathways in the regulation of hematopoiesis under both homeostatic and stress conditions. In particular, the recently discovered cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway is a critical modulator of hematopoiesis. Perturbation of the cGAS-STING pathway in HSPCs may be involved in the pathogenesis of hematopoietic disorders, autoimmune diseases, and inflammation-related diseases and may be candidate therapeutic targets. In this review, we focus on the recent findings of the cGAS-STING pathway in the regulation of hematopoiesis, and its physiopathological significance including its implications in diseases and therapeutic potential.

Keywords: cGAS-STING pathway, Hematopoiesis, Hematopoietic stem and progenitor cells, Cytosolic DNA sensing, Innate Immunity and inflammation

INTRODUCTION

Hematopoietic stem and progenitor cells (HSPCs) in the bone marrow (BM) are responsible for the maintenance of both the homeostatic and stressed hematopoiesis. By modulating the balance between self-renewal and multilineage differentiation, HSPCs give rise to all mature hematopoietic cell types within the blood and immune system, including lymphoid cells, granulocytes, monocytes, dendritic cells (DCs), erythrocytes, and platelets (1). Granulocytes, monocytes, erythrocytes, and platelets are collectively called myeloid cells. Under homeostatic conditions, HSPCs are maintained in a quiescent state in the BM and undergo balanced differentiation into lymphoid and myeloid cells. However, the hematopoietic system is sensitive to stresses, such as infections and genotoxicity, and hematopoietic changes are often the rapid and the first response to stress. Under stress conditions, the quiescent state is disrupted, and HSPCs will biasedly differentiate into specific hematopoietic populations. During these processes, stresses are directly sensed by HSPCs or by HSPC progeny cells and niche cells, which...
in turn modulate hematopoiesis (2). Therefore, HSPCs serve as integrative hubs for the conversion of stress signals into demand-adapted hematopoiesis.

The mechanisms by which HSPCs sense stress have not been completely elucidated; however, it is well-recognized that the recognition of stress-associated molecular patterns and triggering of the immune response are fundamental functions of the immune system (3). Among these pathways, aberrant nucleic acid recognition has been regarded as a key mechanism. The pathways involved in RNA recognition have been reviewed elsewhere (4–6) and will not be covered here. Regarding DNA recognition, Toll-like receptor 9 (TLR9), absent in melanoma 2 (AIM2) and cyclic GMP-AMP synthase (cGAS), are the main specialized receptors that initiate DNA-driven immune responses in mammalian cells (7).

The detection of cytosolic DNA activates the stimulator of interferon genes (STING)-dependent type I interferon (IFN-I)-stimulatory pathway, which is essential for antiviral responses. Generally, the cGAS-STING pathway is required for the IFN-I response triggered by various types of exogenous pathogenic DNA. Loss of the compartmentalization of endogenous DNA, including nuclear DNA (nDNA) and mitochondrial DNA (mtDNA), as well as disturbances in endogenous DNA metabolism also result in cytosolic self-DNA accumulation, which induces immune responses via the cGAS-STING pathway (8–10). Emerging evidence has indicated roles for the cGAS-STING pathway in modulating antitumor immunity (8, 9). Therefore, cellular and organismal homeostasis may be achieved through the recognition of aberrant cytosolic DNA and activation of the cGAS-STING pathway.

Interestingly, based on the transcriptome database, cGAS may be expressed at high levels in HSPCs and even exceed the levels in their certain progeny cells (11). In this review, we primarily focus on the role of the cGAS-STING pathway in hematopoietic regulation and its physiopathological significance. We envision that a better understanding of the stress sensing in HSPCs mediated by the cGAS-STING pathway will help refine potential targets for interventions in patients with hematopoiesis-related diseases.

**THE CGAS-STING PATHWAY**

cGAS is a recently discovered DNA-binding protein that condenses ATP and GTP to synthesize 2′3′-cyclic GMP-AMP (2′3′-cGAMP), which functions as a second messenger that activates STING (12) (Figure 1). In fact, cGAS is not a cytosolic protein but is instead localized to the plasma membrane via the interaction of an N-terminal phosphoinositide-binding domain with phosphatidylinositol 4,5-bisphosphate. The location of cGAS at the plasma membrane ensures the efficient discrimination between self- and non-self-DNA, as cGAS mutants defective in lipid binding induce potent IFN-I responses to genotoxic stress (self-DNA) but weaker responses to viral infection (non-self-DNA) (13). cGAS binds double-stranded DNA (dsDNA) and sometimes single-stranded DNA (ssDNA) via a positively charged surface and its zinc thumb to interact with the DNA (14). The activation of cGAS is also modulated by circular RNA (15), protein interactions (16–18), and posttranslational modifications, including glutamyltylation, ubiquitination, acetylation, and sumoylation (19–23).

Upon activation, STING translocates from the endoplasmic reticulum (ER) membrane to the Golgi and primarily recruits and activates three kinases: TANK-binding kinase 1 (TBK1), which phosphorylates interferon regulatory factor 3 (IRF3); IkB kinase (IKK); and canonical nuclear factor-κB (NF-κB) signaling; and mitogen-activated protein kinase kinase kinase 14 (MAP3K14, best known as NIK), which activates noncanonical NF-κB signaling (Figure 1) (24). TBK1 acts redundantly with IKK to drive NF-κB signaling, and IKKα/IKKβ also activates IRF3 (Figure 1) (25, 26). The cGAS-STING pathway directly or indirectly activates other signaling molecules, such as IRF1, IF5, IRF7, mammalian target of the rapamycin (mTOR), signal transducer and activator of transcription 6 (STAT6), and mitogen-activated protein kinases (MAPKs), including p38, extracellular signal-regulated kinases 1/2 (ERK1/2), and c-Jun-N-terminal kinase (JNK) (Figure 1) (27–33). Consequently, the activated cGAS-STING pathway induces the production of IFN-I and other cytokines involved in the immune response and inflammation. The cGAS-STING pathway is also implicated in the regulation of other important cellular processes, such as autophagy, cell cycle, cell death, and chromosomal stability, to eliminate pathogens, infected cells, or malignantly transformed cells (34–38).

Other sensors, including TLR9 and AIM2, also recognize cytosolic DNA. TLR9 plays a role in DNA sensing in the endosomal compartment and preferentially binds to unmethylated CpG motifs of ssDNA (39), whereas AIM2 senses cytosolic DNA via its C-terminal HIN domain in a sequence-independent manner (Figure 1) (40). Consequently, the ligated TLR9 interacts with its proximal adaptor protein, myeloid differentiation primary response 88 (MyD88), to activate TRAF6 and MAPKs (41); activated AIM2 associates with the adaptor molecule apoptosis-associated speck-like protein containing caspase recruitment domain (ASC), to form an inflammasome complex, which activates gasdermin D (GSDMD)-mediated pyroptosis and caspase 1 (CASP1)-dependent maturation of interleukin 1β (IL1β) (Figure 1) (40, 42). However, both TLR9 and AIM2 are dispensable for IFN-I induction, suggesting a central role of the cGAS-STING pathway in cytosolic DNA sensing.

**Abbreviations:** AIM2 absent in melanoma 2 caspase 1; CDN: cyclic dinucleotides; cGAS: cyclic GMP-AMP synthase; CPMs: common myeloid progenitors; DCs: dendritic cells; DDR: DNA damage response; GMPs: granulocyte-monocyte progenitors; GSDMD: gasdermin D; HSCs: hematopoietic stem cells; HSPCs: hematopoietic stem and progenitor cells; IFN- I: type I interferon; IL1β: interleukin 1β; IKK: IkB kinase; JNK: c-Jun-N-terminal kinase; MDS: myelodysplastic syndromes; MDPs: monocyte-dendritic cell progenitors; MyD88: myeloid differentiation primary response 88; NF-κB: nuclear factor-κB; NLRP3: NOD-, LRR-, and pyrin domain-containing protein 3; STING: stimulator of interferon genes; TBK1: TANK-binding kinase 1; TLR9: Toll-like receptor 9; TRAF6: TNF receptor associated factor 6; PARP1: poly (ADP-ribose):; polymerase 1; PUMA: p53 upregulated modulator of apoptosis.
Upon stresses, such as infections and genotoxicity, a considerable number of hematopoietic cells, especially myeloid cells, are depleted. The hematopoietic system needs to respond rapidly to replenish myeloid cells via a process called “emergency myelopoiesis” (43). According to recent studies, HSPCs may be the central hub of stress responses (43–48). HSPCs are able to skip several steps in the traditional tree-like hematopoietic hierarchy and directly differentiate into myeloid progenitor cells (49–51). Meanwhile, hematopoietic stem cells (HSCs) are heterogeneous, and myeloid-biased HSC subtypes may selectively expand in response to stress (52). Through these mechanisms, the hematopoietic system rapidly satisfies the increased demand for myeloid cells during stress. Therefore, the rapid myeloid-biased differentiation of HSPCs is required for the hematopoietic system to adapt to stresses. Although the cGAS-STING pathway is essential for sensing and defending against stresses, its role in regulation hematopoiesis has rarely been examined. The present review summarizes the role of the cGAS-STING pathway to obtain a better understanding of the mechanism regulating hematopoiesis (Figure 2).

THE CGAS-STING PATHWAY IN STEADY-STATE HEMATOPOIESIS

A circular RNA named cia-cGAS was recently reported to be expressed at high levels in the nuclei of HSCs. Cia-cGAS displays a stronger binding affinity for cGAS than self-DNA. Cia-cGAS binds cGAS in the nucleus to block its synthase activity under steady-state condition, while a cia-cGAS deficiency will lead to increased expression of IFN-I in the BM but decreased numbers of dormant HSCs. Therefore, cia-cGAS suppresses the cGAS-mediated production of IFN-I in HSCs and the exhaustion of dormant HSCs (15). R-loops, the nucleic acid structures consisting of displaced ssDNAs and RNA : DNA hybrids, also activate cGAS-STING pathway in HSPCs. DEAD-box Helicase 41 (DDX41) binds R-loops and acts as a suppressor of R-loop accumulation. DDX41 insufficiency will result in excessive R-loop accumulation, which subsequently activate the cGAS-STING-NF-κB pathway to promote HSPC expansion via secreting inflammatory cytokines (Table 1) (53). Meanwhile, BAK/BAX-mediated apoptosis will trigger the release of mtDNA, which is
recognized by the cGAS-STING pathway. The subsequent production of IFN-I in hematopoietic cells will expand HSCs but suppress their self-renewal capacity (Table 1). However, caspase activation following BAK/BAX activation will attenuate the IFN-I response possibly through global cellular demolition (54). In addition, gain-of-function STING mutation-induced constitutive activation of the cGAS-STING pathway causes myeloid cell expansion and lymphoid cell cytopenia in an IRF3-independent manner (75, 76). Of note, in this case, the HSC pool is only moderately affected, whether HSC function such as self-renewal capacity is influenced remains unknown (76).

**REGULATION OF HSPC MAINTENANCE BY THE CGAS-STING PATHWAY**

The cGAS-STING pathway directly and indirectly regulates cell activities, including proliferation, differentiation, cell death, autophagy, senescence, and metabolism, through the activation of its downstream effectors or the secretion of cytokines. However, evidence for whether and how this pathway regulates HSPC maintenance is scarce. We discuss the recently discovered functions of the cGAS-STING pathway and its potential roles in regulating HSPC maintenance.

Downstream effectors of the cGAS-STING pathway, including IRFs, NF-κB, mTOR, and MAPKs, are closely associated with hematopoiesis. The roles of mTOR and MAPKs in HSPC maintenance are well-defined (Table 1) (29, 64–66). IRFs and NF-κB are transcription factors, and their activation directly modulates hematopoiesis at the genetic level. IRF1, IRF3, IRF5, and IRF7 act downstream of the cGAS-STING pathway (31–33, 55, 77). IRF2 represses IRF1 by competitively binding to the promoter of target genes. IRF1 activation and IRF2 deficiency promote the proliferation of HSCs but reduce their self-renewal capacity (Table 1) (56). IRF3 is implicated in infection-associated HSC proliferation and a reduction in self-renewal (55). IRF5 may participate in the mechanism regulating HSPC survival, because a deletion of IRF5 protects HSPCs from DNA damage-induced apoptosis (Table 1) (57). IRF7 activation reduces HSC populations in the aorta-gonad-mesonephros (AGM) region and the T cell differentiation of HSCs, suggesting roles for IRF7 in HSC development and specification (Table 1) (58). These data suggest distinct functions of IRFs in regulating HSC maintenance. NF-κB promotes the myeloid differentiation of HSCs through the transcriptional activation of the myeloid transcription factor PU.1 (Table 1) (59). However, a reduction in basal NF-κB signaling induced by a TRAF6 or IKK deficiency promotes proliferation and myeloid-biased differentiation but reduces the self-renewal of HSCs under homeostatic conditions (Table 1) (63).

The most important function of the cGAS-STING pathway is the production of various cytokines and chemokines. HSPCs and their progeny and niche cells contribute to cytokine production during stress. Notably, the ability of HSPCs to produce cytokines exceeds their progeny cells in both magnitude and breadth (48). Given the high expression of cytokine and chemokine receptors, cytokines and chemokines may help HSPCs rapidly adapt to stresses in an autocrine manner. Here, we discuss the most common cytokines downstream of the cGAS-STING pathway, including IFN-1, Interleukin-1 (IL-1), IL-6, and TNF.

IFN-1 is the hallmark cytokine produced following the activation of the cGAS-STING pathway. Acute IFN-1 signaling promotes HSC proliferation but reduces the self-renewal capacity and mobilization of HSCs (Table 1) (55, 56, 67, 68). IFN-1 signaling increases the phosphorylation of STAT1 and Akt/mTOR and upregulates the
### Roles of stress-related pathways including the cGAS-STING pathway in regulating HSPC maintenance.

| Species | Context | Target | Target cells | Outcome | Mechanism | Reference |
|---------|---------|--------|--------------|---------|-----------|-----------|
| Mouse | Homeostasis | cGAS-STING pathway | HSCs | Proliferation; Reduced self-renewal | Cia-cGAS is a suppressor of cGAS. Cia-cGAS deficiency results in the hyperactivation of cGAS-STING pathway and increased production of IFN-I. | (15) |
| Mouse | Homeostasis | cGAS-STING pathway | HSPCs | Proliferation | DDX41 insufficiency results in excessive R-loop accumulation, which subsequently activate cGAS-STING-NF-κB pathway to promote HSPC expansion. | (53) |
| Mouse | Homeostasis | cGAS-STING pathway | HSCs | Proliferation; Reduced self-renewal | Apoptotic caspases deficiency triggers the release of mtDNA, which induces the constitutive activation of cGAS-STING pathway and increased IFN-I production. | (54) |
| Mouse | c-di-GMP administration | cGAS-STING pathway | HSPCs | Proliferation; Myeloid-biased differentiation; Mobilization; Reduced self-renewal | Bacterial c-di-GMP activates STING pathway in a cGAS-independent manner, the downstream IRF3/IFN-I signaling induces HSPC proliferation and myeloid-biased differentiation but reduces HSC self-renewal and mobilization; the downstream NF-κB/G-CSF and JNK/TGF-β promotes HSC mobilization. | (55) |
| Mouse | Homeostasis | IRF1/IRF2 | HSCs | Proliferation; Reduced self-renewal | IRF1 is a downstream effector of both cGAS-STING pathway and IFN-I signaling. IRF2 can repress IRF1 through competitively binding to the promoter of target genes. IRF1 activation or IRF2 deficiency will promote proliferation but reduce self-renewal of HSCs. | (56) |
| Mouse | Genotoxic stress (IR) | IRF5 | HSPCs | Proliferation | IRF5 is a downstream effector of both cGAS-STING pathway and IFN-I signaling. IRF5 is upregulated and may contribute to increased proliferation, replication stress, and apoptosis of HSPC after IR. | (57) |
| Mouse; Zebrafish | Homeostasis | IRF7 | HSCs | Myeloid-biased differentiation; Reduced self-renewal | IRF7 is a downstream effector of both cGAS-STING pathway and IFN-I signaling. IRF7 activation will reduce HSC formation in the AGM region and T cell differentiation of HSCs. | (58) |
| Human; Mouse | Infection; Inflammation | NF-κB | HSCs | Proliferation; Myeloid-biased differentiation; Reduced self-renewal | NF-κB is a main downstream effector of both cGAS-STING pathway and cytokine signaling such as IL1 and TNF. NF-κB can induce the transcriptional activation of myeloid transcription factor PU.1. | (59–62) |
| Mouse | Homeostasis | TRAF6/IKK/NF-κB | HSCs | Proliferation; Myeloid-biased differentiation; Reduced self-renewal | TRAF6 or IKK deficiency-induced reduction of basal NF-κB signaling can promote proliferation and myeloid-biased differentiation but reduce self-renewal of HSCs. | (63) |
| Human; Mouse | Homeostasis; Stress | mTOR or MAPKs | HSCs | Proliferation; Myeloid-biased differentiation; Reduced self-renewal | mTOR or MAPKs signaling activation is associated with increased proliferation and myeloid-biased differentiation, but reduced self-renewal of HSCs. | (29, 64–66) |
| Mouse | pH3 administration | IFN-I signaling | HSPCs | Proliferation; Myeloid-biased differentiation; Reduced self-renewal | Acute IFN-I signaling activates STAT1 and Akt/mTOR to upregulate the expression of Sca-1 and myeloid markers in HSPCs. Besides, IFN-I can also upregulate IRFs in a positive feedback manner. | (55, 56, 67–69) |
| Mouse; Zebrafish | Homeostasis; LPS and Pam3CSK4 administration | IL-6 signaling | HSPCs | Proliferation; Myeloid-biased differentiation; Reduced self-renewal | IL-6 signaling may engage the Akt/mTOR and SHP2/STAT3 pathway to modulate HSPC maintenance. Besides, it is a particularly important modulator in mediating rapid myeloid cell recovery during chemotherapy-induced neutropenia. | (48, 70, 71) |
| Mouse | Transplantation; Inflammation | TNF signaling | HSCs | Reduced clonal growth and self-renewal | TNF can strongly inhibit the clonal growth and compromise the repopulation capacity of HSCs that engages its two distinct receptors. | (72) |

(Continued)
expression of stem cell antigen-1 (Sca-1) and myeloid markers, such as CD41. Conversely, inhibition of STAT1, Akt/mTOR, or Sca-1 will cause HSCs to become insensitive to IFN-I stimulation, indicating that STAT1, Akt/mTOR, and Sca-1 mediate the effects of IFN-I (67, 68). IFN-I also upregulates IRFs through a positive feedback mechanism (69), which may in turn regulate HSPC maintenance, as described above. However, chronic IFN-I signaling inhibits HSC proliferation and triggers apoptosis mediated by p53 and the receptor-interacting protein kinase-1 (RIPK1)-CASP8 pathway-mediated or RIPK3- and mixed-lineage kinase domain-like protein (MLKL)-mediated necroptosis of HSCs, leading to HSC exhaustion (Table 1) (36, 73, 74, 78). Notably, IFN-I signaling-induced mitochondrial reactive oxygen species (ROS) overproduction causes DNA damage in HSCs (Table 1) (46), which provides a novel connection between stress hematopoiesis and the occurrence of DNA damage and decreased function of adult HSCs.

IL-1 promotes the proliferation and myeloid-biased differentiation of HSCs and prevents chemotherapy-mediated myelosuppression by activating the NF-κB–PU.1 axis, but it mitigates the self-renewal capacity of HSCs (Table 1) (59–61). Similarly, IL-6 also promotes HSPC proliferation and myeloid-biased differentiation in an autocrine or paracrine manner (Table 1) (48, 70, 71). In particular, Zhao et al. identified IL-6 as a particularly important modulator that mediates rapid myeloid cell recovery during chemotherapy-induced neutropenia (48).

TNF overproduction is closely associated with the BM hematopoietic failure observed in many patients with acute or chronic inflammatory diseases. TNF strongly inhibits clonal growth and compromises the repopulation capacity of HSCs (72). Notably, actively cycling rather than quiescent HSCs are the primary targets of TNF-mediated hematopoietic suppression (Table 1) (72). The latest research has revealed different effects of TNF on HSCs, and myeloid progenitors are actually different. TNF prevents HSC necroptosis and promotes myeloid-biased differentiation via the NF-κB-dependent transcriptional activation of cellular inhibitor of apoptosis protein 2 (cIAP2) and PU.1, respectively, whereas it induces myeloid progenitor apoptosis. Consequently, TNF-α prevents the necroptosis, but not apoptosis, of HSPCs and poises HSPCs for myeloid cell production but kills other blood cells, which facilitates hematopoietic clearance and promotes regeneration in response to inflammatory stress (Table 1) (62).

**THE CGAS-STING PATHWAY IN STRESSED HEMATOPOIESIS**

**Infection**

The cGAS-STING pathway protects against infections with viruses, bacteria, and protozoan parasites by sensing pathogenic DNA, infection-induced mitochondrial damage, bacterial proteins, virulence factors and metabolites, and bacteria-derived cyclic dinucleotides (CDNs) (79–84). Meanwhile, infected cells transactivate the cGAS-STING pathway in bystander cells via the cell-to-cell transmission of cGAMP or the release of extracellular vesicles (EVs) (85–89). Based on accumulating evidence, HSPCs, and not only their progeny immune cells, are able to directly sense and respond to infections. For example, HSPCs directly sense a mimic of viral nucleic acid, polyinosinic-polycytidylic acid (pI:C), to elicit IFN-I production through a process independent of TLR signaling (68). Meanwhile, HSPCs were recently shown to sense one of the CDNs, c-di-GMP, via STING. Upon c-di-GMP exposure, STING activation in HSPCs induces HSC entry into the cell cycle and promotes HSPC proliferation and mobilization, but it decreases the number and repopulation capacity of LT-HSC (55). On the other hand, HSPCs indirectly recognize the acute or chronic infectious state by sensing the extrinsic signals, such as the cytokines or chemokines released by their progeny immune cells, niche cells, or themselves (Figure 2). In particular, the abundance of these receptors on HSPCs increases significantly during systemic infections (48).

**Genotoxic Stress**

Genotoxic stress is derived from a wide variety of physical and chemical sources, such as ionizing radiation, chemotherapeutic agents, and mutagenic agents. In fact, the long-living property of HSCs makes these cells particularly susceptible to genotoxic stress. HSCs are thought to be the gatekeeper of genomic integrity of the entire hematopoietic system, because an unrepaired genetic lesion in a single HSC may spread throughout the HSC pool and propagate to all of the hematological compartments via self-renewing division and differentiation (90). DNA damage occurs when cells are exposed to genotoxic stress. In fact, HSPCs are sensitive to genotoxic stress-induced DNA damage, including DSBs and micronuclei formation (91). Recent advances suggest that the cGAS-STING pathway may play an essential role in the genotoxic stress of HSPCs by sensing DSBs and micronuclei (91–94). Therefore, reacquainting the role of the cGAS-STING pathway in HSPC (Table 1) maintenance under
The cGAS-STING pathway in HSPCs may be employed as a therapeutic target or to develop vaccine adjuvants for chronic infections. Activation of the cGAS-STING pathway may promote the myeloid-biased differentiation of HSPCs to enhance the anti-infection reservoir of the immune system. However, it should bear in mind that the activation of the cGAS-STING pathway may also increase the vulnerability to or severity of infections through dampening adaptive immunity, exacerbating inflammation or facilitating pathogen replication, survival, and infection (81, 108–113).

HSPC maintenance is closely associated with the pathogenesis of autoimmune diseases. HSPCs confer protection to secondary infection, in a phenomenon termed “trained innate immunity” or “innate immune memory,” which contributes to autoimmune diseases through exaggerating immune responses (114–116). Meanwhile, the myeloid progenitors released from the BM may infiltrate peripheral tissues and produce primed neutrophils in situ to exacerbate inflammatory responses within the affected tissues (117, 118). On the other hand, patients with autoimmune diseases may have a poor response to infectious challenges due to the deficiency of lymphoid cells (119). During these processes, the cGAS-STING pathway in HSPCs may play an important role.

Myelopoiesis or lymphocytopenia are closely associated with inflammation-related diseases including gain-of-function STING mutation-induced vasculopathy, cardiovascular diseases (CVD), and metabolic diseases (75, 120–126). Conversely, the modulation of HSPC maintenance that reduces myeloid cell production can protect against CVD (127, 128). Therefore, the cGAS-STING pathway in HSPCs may be a promising target to provide new insights into the pathogenesis and treatment of inflammation-related diseases.

The cGAS-STING pathway has been considered as a promising immunotherapy target in recent years (8). Synergetic effects can be achieved in multiple tumors using the combination immunotherapies with cGAS-STING pathway agonists (129, 130). However, the activated cGAS-STING pathway may promote growth or metastasis of certain tumors (131), and its chronic activation paradoxically induces an immune-suppressive tumor microenvironment by promoting the myeloid-biased differentiation of HSPCs and apoptosis of T cells (95). Individualized or specific cell-targeted application of cGAS-STING pathway agonists or antagonists will be feasible in the future.

**CONCLUSIONS**

Although the immunomodulatory effects of the cGAS-STING pathway in hematopoietic cells have been extensively studied, little attention has been paid to its roles in hematopoiesis. The regulation of HSPC maintenance is an attractive field to understand hematopoiesis under homeostatic and stress conditions. Components of the cGAS-STING pathway may be expressed at high levels in HSPCs, which may allow HSPCs to rapidly sense and respond to stresses, including infection and genotoxicity, by promoting HSPC proliferation, mobilization, and myeloid-biased differentiation (Figure 2). Moreover, this rapid response may also facilitate the elimination of damaged HSPCs or malignant cell-targeted application of cGAS-STING pathway agonists or antagonists will be feasible in the future.
transformed HSPCs via the induction of cell death to maintain the fitness of the HSPC pool. On the other hand, modulation of the cGAS-STING pathway in HSPCs may boost anti-infection or antitumor immunity and suppress autoimmunity and peripheral inflammation. However, multiple obstacles must be addressed before its clinical application. For example, chronic activation of the cGAS-STING pathway may promote the pathogenesis of myeloid malignancies or induce an adaptive immunodeficiency. Future studies aiming to discover the distinct functions of the cGAS-STING pathway in HSPC maintenance and develop modulators targeting specific cell types will be meaningful.

REFERENCES

1. Pinho S, Frenette PS. Haematopoietic stem cell activity and interactions with the niche. *Nat Rev Mol Cell Biol* (2019) 20(3):303–20. doi: 10.1038/s41580-019-0103-9
2. Chavakis T, Mitroulis I, Hajishengallis G. Hematopoietic progenitor cells as integrative hubs for adaptation to and fine-tuning of inflammation. *Nat Immunol* (2019) 20(7):802–11. doi: 10.1038/s41590-019-0402-5
3. Taguchi T, Mukai K. Innate immune signalling and membrane trafficking. *Curr Opin Cell Biol* (2019) 59:1–7. doi: 10.1016/j.cceb.2019.02.002
4. Rehwinkel J, Gack MU. RIG-I-like receptors: their regulation and roles in RNA sensing. *Nat Rev Immunol* (2020) 20(9):537–51. doi: 10.1038/s41577-020-0288-3
5. Ablasser H, Hsu R. Regulation of cGAS- and RLR-mediated immunity to nucleic acids. *Nat Immunol* (2020) 21(1):17–29. doi: 10.1038/s41590-019-0556-1
6. Tatematsu M, Funami K, Seya T, Matsumoto M. Extracellular RNA Sensing by Pattern Recognition Receptors. *J Innate Immun* (2018) 10(5-6):398–406. doi: 10.1159/000490434
7. Vanpouille-Box C, Demaria S, Formenti SC, Galluzzi L. Cytosolic DNA Sensing in Organisal Tumor Control. *Cell Cancer* (2018) 34(3):361–78. doi: 10.1016/j.jcell.2018.05.013
8. Motwani M, Pesiridis S, Fitzgerald KA. DNA sensing by the cGAS-STING pathway in health and disease. *Nat Rev Genet* (2019) 20(11):657–74. doi: 10.1038/s41576-019-0151-1
9. Ablasser H, Chen ZJ. cGAS in action: Expanding roles in immunity and inflammation. *Science* (2019) 363(6431):eaat8657. doi: 10.1126/science.aat8657
10. Guey B, Wischniewski M, Decout A, Makasheva K, Kaynak M, Sakar MS, et al. BAF restricts cGAS on nuclear DNA to prevent innate immune activation. *Sci (N Y) NY* (2020) 369(6505):823–8. doi: 10.1126/sciadv.aaw6421
11. Qian P, He XC, Paulson A, Li Z, Tao F, Perry JM, et al. The Ilk1–Gtl2 Locus Preserves LT-HSC Function by Inhibiting the PI3K-mTOR Pathway to Restrict Mitochondrial Metabolism. *Cell Stem Cell* (2016) 18(2):214–28. doi: 10.1016/j.stem.2015.11.001
12. Sun L, Wu J, Du F, Chen X, Chen ZJ. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. *Science* (2013) 339(6121):786–91. doi: 10.1126/science.1232458
13. Barnett KC, Coronas-Serna JM, Zhou W, Ernandes MJ, Cao A, Kranzusch PJ, et al. Phosphoinositide Interactions Position cGAS at the Plasma Membrane to Ensure Efficient Distinction between Self- and Viral DNA. *Cell* (2019) 176(6):1432–46.e11. doi: 10.1016/j.cell.2019.01.049
14. Cai X, Chiu YH, Chen ZJ. Innate immunity signalling and membrane trafficking. *Nat Rev Immunol* (2016) 17(4):369–78. doi: 10.1038/nri.3356
15. Galluzzi L, Vanpouille-Box C, Bakhoun SF, Demaria S. SnapShot: CGAS-STING Signaling. *Cell* (2018) 171(3):276–81. doi: 10.1016/j.cell.2018.03.015
16. Balka KR, Louis C, Saunders TL, Smith AM, Calleja DJ, D’Silva DB, et al. TBK1 and IKKε Act Redundantly to Mediate STING-Induced NF-kB Responses in Myeloid Cells. *Cell Rep* (2020) 31(1):107492. doi: 10.1016/j.celrep.2020.03.056
17. Yu Q, Katlinskaya YV, Carbone CJ, Zhao B, Katlinski KV, Zheng H, et al. DNA-damage-induced type I interferon promotes senescence and inhibits stem cell function. *Cell Rep* (2015) 11(5):785–97. doi: 10.1016/j.celrep.2015.03.090
18. Bodur C, Kazyken D, Huang K, Ekim Ustunel B, Siroky KA, Tooley AS, et al. The IKK-related kinase TBK1 activates mTORC1 directly in response to growth factors and innate immune agonists. *EMBO J* (2018) 37(1):19–38. doi: 10.15252/embj.201696164
19. Chen H, Sun H, You F, Sun W, Zhou X, Chen L, et al. Activation of STAT6 by STING is critical for antiviral innate immunity. *Cell* (2011) 147(2):436–46. doi: 10.1016/j.cell.2011.09.022
20. Wang YY, Shen D, Zhao JJ, Zeng N, Hu TH. Sting is a critical regulator of type I interferon responses in myeloid cells. *Cell Rep* (2019) 25(4):1074–92. doi: 10.1016/j.celrep.2019.07.075
21. Luo X, Li H, Ma L, Zhou J, Guo Y, 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. doi: 10.1053/j.gastro.2018.09.010
22. Park SM, Omatsu T, Zhao Y, Yoshida N, Shah P, Zagani R, et al. T cell fate following Salmonella infection is determined by a STING-IRF1 signaling axis in mice. *Commun Biol* (2019) 2:464. doi: 10.1038/s42003-019-0701-2
23. Andzinskas I, Spanier J, Kasznit N, Kröger A, Jin L, Brinkmann MM, et al. Growing tumors induce a local STING-dependent Type I IFN response in dendritic cells. *Int J Cancer* (2016) 139(6):1350–7. doi: 10.1002/ijc.31059

AUTHOR CONTRIBUTIONS

CD and JW decided on the topics. WL and CD wrote the manuscript and prepared the figures and the table. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Natural Science Foundation of China (No. 81725019, 81930090, 81874256).

Frontiers in Immunology | www.frontiersin.org November 2020 | Volume 11 | Article 5739158

Liao et al. The cGAS-STING Pathway in Hematopoiesis
Liao et al. The cGAS-STING Pathway in Hematopoiesis

88. Choudhuri S, Garg NJ. PARP1-cGAS-NF-

89. Cheng Y, Schorey JS. Mycobacterium tuberculosis-induced IFN-

78. Sarhan J, Liu BC, Muendlein HI, Weindel CG, Smirnova I, Tang AY, et al. Nucleic

75. Warner JD, Irizarry-Caro RA, Bennion BG, Ai TL, Smith AM, Miner CA,

76. Bouis D, Kirstetter P, Arbogast F, Lamon D, Delgado V, Jung S, et al. Severe

79. Lahaye X, Gentili M, Silvin A, Conrad C, Picard L, Jouve M, et al. NONO

80. Scumpia PO, Botten GA, Norman JS, Kelly-Scumpia KM, Sprea

84. Kim BR, Kim BJ, Kook YH, Kim BJ. Mycobacterium abscessus infection

12. doi: 10.1038/s12276-019-0320-5

7. doi: 10.1084/jem.2015102718

68. doi: 10.1111/febs.15001

55. doi: 10.1038/natrevmolcellbio.2018.4

56. doi: 10.1038/nature25154

59. Mandal PK, Blanpain C, Rossi DJ. DNA damage response in adult stem cells: pathways and consequences. Nat Rev Mol Cell Biol (2011) 12(3):198–202. doi: 10.1038/nrm3060

50. Garaycochea JI, Crossan GP, Langevin F, Mulderigg L, Louzada S, Yang F, et al. Alcohol and endogenous aldehydes damage chromatin and mutate stem cells. Nature (2018) 553(7687):171–7. doi: 10.1038/nature25154

49. doi: 10.1038/s41586-018-0629-6

48. doi: 10.1038/nature21388

47. doi: 10.1038/nature20191015

46. doi: 10.1038/nature23449

45. doi: 10.1038/nature20171351

44. doi: 10.1080/09602641.2019.959087

43. doi: 10.1084/jem.20171351

42. doi: 10.1038/ncomms12276

41. doi: 10.1038/nature23470

40. doi: 10.1038/s41586-019-0885-0

39. doi: 10.1038/s41564-019-0367-z

38. doi: 10.1038/s41586-019-0320-5

37. doi: 10.1038/s41586-018-0186-0

36. doi: 10.1038/s41564-019-0363-x

35. doi: 10.1038/jem.20180508

34. doi: 10.1038/natrevmolcellbio.2018.4

33. doi: 10.1084/jem.20180508

32. doi: 10.1038/s41586-019-0186-0

31. doi: 10.1111/febs.15001

30. doi: 10.1101/jcell.2018.10.0862

29. doi: 10.1038/s41586-018-0186-0

28. doi: 10.1038/nature23449

27. doi: 10.1038/nature23470

26. doi: 10.1038/nature15001

25. doi: 10.1038/natrevmolcellbio.2018.4

24. doi: 10.1038/jem.2019102718

23. doi: 10.1038/nature15001

22. doi: 10.1038/jem.2019102718

21. doi: 10.1038/nature23449

20. doi: 10.1038/nature23449

19. doi: 10.1038/nature21388

18. doi: 10.1128/jvi.01102-18

17. doi: 10.1038/nature201808062

16. doi: 10.1038/nature21388

15. doi: 10.1038/nature25154

14. doi: 10.1038/s41586-018-0186-0

13. doi: 10.1038/s41586-019-0186-0

12. doi: 10.1038/s41586-019-0885-0

11. doi: 10.1038/nature25154

10. doi: 10.1038/nature20191015

9. doi: 10.1038/ncomms12276

8. doi: 10.1038/jem.20180508

7. doi: 10.1038/s41586-018-0186-0

6. doi: 10.1038/nature20191015

5. doi: 10.1038/nature23449

4. doi: 10.1038/nature21388

3. doi: 10.1038/nature25154

2. doi: 10.1038/nature201808062

1. doi: 10.1038/nature21388

The cGAS-STING Pathway in Hematopoiesis

Trypanosoma cruzi infection and Chagas disease. PloS Pathog (2020) 16 (4):e1008474. doi: 10.1371/journal.ppat.1008474

Mandal PK, Blanpain C, Rossi DJ. DNA damage response in adult stem cells: pathways and consequences. Nat Rev Mol Cell Biol (2011) 12(3):198–202. doi: 10.1038/nrm3060

Garaycochea JI, Crossan GP, Langevin F, Mulderigg L, Louzada S, Yang F, et al. Alcohol and endogenous aldehydes damage chromatin and mutate stem cells. Nature (2018) 553(7687):171–7. doi: 10.1038/nature25154

Shao L, Luo Y, Zhou D. Hematopoietic stem cell injury induced by ionizing radiation. Antioxid Redox Signal (2014) 20(9):1447–62. doi: 10.1089/ars.2013.3635

Harding SM, Benc LJI, Irianto J, Discher DE, Minn AJ, Greenberg RA. Mitotic progression following DNA damage enables pattern recognition within microenvironments. Nature (2017) 548(7668):466–70. doi: 10.1038/nature23470

Mackenzie KJ, Carroll P, Martin CA, Murina O, Flateau A, Simpson DJ, et al. cGAS surveillance of microenvironments leads to innate immune responses. Connexin-Dependent Transfer of cGAMP to Phagocytes Modulates Antiviral Responses. Sci Rep (2018) 8(1):9825. doi: 10.1038/s41598-019-45800-0

Connexin-Dependent Transfer of cGAMP to Phagocytes Modulates Antiviral Responses. Sci Rep (2018) 8(1):9825. doi: 10.1038/s41598-019-45800-0

Choudhuri S, Garg NJ. PARP1-cGAS-NF-κB pathway of proinflammatory macrophage activation by extracellular vesicles released during
110. Heipertz EL, Harper J, Walker WE. STING and TRIF Contribute to Mouse Sepsis, Depending on Severity of the Disease Model. Shock (2017) 47(5):621–31. doi: 10.1097/shk.0000000000000771

111. Bennion BG, Ingle H, Ai TL, Miner CA, Platt DJ, Smith AM, et al. A Human Gain-of-Function STING Mutation Causes Immunodeficiency and Gammaherpesvirus-Induced Pulmonary Fibrosis in Mice. J Virol (2019) 93(4):142(3):e01806–18. doi: 10.1128/jvi.01806-18

112. Majumdar T, Chattopadhyay S, Ozhegov E, Dhar J, Goswami R, Sen GC, et al. Induction of interferon-stimulated genes by IRF3 promotes replication of Toxoplasma gondii. PloS Pathog (2015) 11(3):e1004779. doi: 10.1371/journal.ppat.1004779

113. Guimarães ES, Gomes MTR, Campos PC, Mansur DS, Dos Santos AA, Fermaintt CS, Sano K, Liu Z, Ishii N, Seino J, Dobbs N, et al. A bioactive mammalian disaccharide associated with autoimmunity activates STING-TBK1-dependent immune response. Nat Commun (2019) 10(1):2377. doi: 10.1038/s41467-019-10319-5

114. Kumar V. A STING to inflammation and autoimmunity. J Leukoc Biol (2019) 106(1):171–85. doi: 10.1002/jlb.1018-397rr

115. Vanpouille-Box C, Hoffmann JA, Galluzzi L. Pharmacological modulation of nucleic acid sensors - therapeutic potential and persisting obstacles. Nat Rev Drug Discovery (2019) 18(11):845–67. doi: 10.1038/s41573-019-0043-2

116. Cairns AP, Crockard AD, McConnell JR, Courtney PA, Bell AL. Reduced expression of CD44 on monocytes and neutrophils in systemic lupus erythematosus: relations with apoptotic neutrophils and disease activity. Ann Rheum Dis (2001) 60(10):950–5. doi: 10.1136/ard.60.10.950

117. Orr Y, Taylor JM, Bannon PG, Gecky C, Krishdarss L. Circulating CD10+CD16low neutrophils provide a quantitative index of active bone marrow neutrophil release. Br J Haematol (2005) 131(4):508–19. doi: 10.1111/j.1365-2411.2005.05197.x

118. Bach JF. The hygiene hypothesis in autoimmunity: the role of pathogens and commensals. Nat Rev Immunol (2018) 18(2):105–20. doi: 10.1038/nri.2017.111

119. Luksch H, Stinson WA, Platt DJ, Qian W, Kalugotla G, Miner CA, et al. STING-associated lung disease in mice relies on T cells but not type I interferon. J Allergy Clin Immunol (2019) 144(1):254–66.e8. doi: 10.1016/j.jaci.2019.01.044

120. Quail DL, Olson OC, Bhardwaj P, Walsh LA, Akkari L, Quick ML, et al. Obesity alters the lung myeloid cell landscape to enhance breast cancer metastasis through IL5 and GM-CSF. Nat Cell Biol (2017) 19(8):974–87. doi: 10.1038/ncl2b3578

121. Barrett TJ, Distel E, Murphy AJ, Hu J, Garshick MS, Ogando Y, et al. Apolipoprotein A1 Promotes Atherosclerosis Regression in Diabetic Mice by Suppression of Myelopoiesis and Plaque Inflammation. Circulation (2019) 140(4):1170–84. doi: 10.1161/circulationaha.118.039476

122. Nakamura K. Myeloid cell contributions to cardiovascular health and disease. Nat Med (2018) 24(6):711–20. doi: 10.1038/s41591-018-0064-0

123. Murphy AJ, Tall AR. Disordered haematopoiesis and athero-thrombosis. Eur Heart J (2016) 37(14):1113–21. doi: 10.1093/eurheartj/ehv718

124. Rohde SF, Zhuang X, Coppen I, Vasamsetti SB, Modugu G, Schloss MJ, et al. Bone Marrow Endothelial Cells Regulate Myelopoiesis in Diabetes. Circulation (2020) 142(3):244–58. doi: 10.1161/circulationaha.120.046038

125. Sreejith G, Abdel-Latif A, Athmanathan B, Annabathula R, Dhyani A, Noothi SK, et al. Neutrophil-Derived S100A8/A9 Amplify Granulopoiesis After Myocardial Infarction. Circulation (2020) 141(13):1080–94. doi: 10.1161/circulationaha.119.043833

126. Orr Y, Bagnon PG, Gecky C, Krishdarss L. Circulating CD10+CD16low neutrophils provide a quantitative index of active bone marrow neutrophil release. Br J Haematol (2005) 131(4):508–19. doi: 10.1111/j.1365-2411.2005.05197.x

127. McAlpine CS, Saeed A, Ruan X, Guan H, Su J, Ouyang S. Regulation of cGAS-Mediated Immune Responses and Immunotherapy. Trends Mol Med (2019) 25(5):412–27. doi: 10.1016/j.molmed.2019.02.007

128. Sreejith G, Abdel-Latif A, Athmanathan B, Annabathula R, Dhyani A, Noothi SK, et al. Neutrophil-Derived S100A8/A9 Amplify Granulopoiesis After Myocardial Infarction. Circulation (2020) 141(13):1080–94. doi: 10.1161/circulationaha.119.043833

129. Barker TJ, Distel E, Murphy AJ, Hu J, Garshick MS, Ogando Y, et al. Apolipoprotein A1 Promotes Atherosclerosis Regression in Diabetic Mice by Suppression of Myelopoiesis and Plaque Inflammation. Circulation (2019) 140(4):1170–84. doi: 10.1161/circulationaha.118.039476

130. Nahrendorf M. Myeloid cell contributions to cardiovascular health and disease. Nat Med (2018) 24(6):711–20. doi: 10.1038/s41591-018-0064-0

131. Murphy AJ, Tall AR. Disordered haematopoiesis and athero-thrombosis. Eur Heart J (2016) 37(14):1113–21. doi: 10.1093/eurheartj/ehv718

132. Rohde SF, Zhuang X, Coppen I, Vasamsetti SB, Modugu G, Schloss MJ, et al. Bone Marrow Endothelial Cells Regulate Myelopoiesis in Diabetes. Circulation (2020) 142(3):244–58. doi: 10.1161/circulationaha.120.046038

133. Sreejith G, Abdel-Latif A, Athmanathan B, Annabathula R, Dhyani A, Noothi SK, et al. Neutrophil-Derived S100A8/A9 Amplify Granulopoiesis After Myocardial Infarction. Circulation (2020) 141(13):1080–94. doi: 10.1161/circulationaha.119.043833

134. McAlpine CS, Saeed A, Ruan X, Guan H, Su J, Ouyang S. Regulation of cGAS-Mediated Immune Responses and Immunotherapy. Adv Sci (Weinh) (2020) 7(6):1902599. doi: 10.1002/ads.201902599

135. Bakhom SF, Ngo B, Laughney AM, Cavallo JA, Murphy CJ, Ly P, et al. Sleep modulates haematopoiesis and protects against atherosclerosis. Nature (2019) 566(7744):383–7. doi: 10.1038/s41586-019-0948-2

136. Frodermann V, Rohde D, Courties G, Severe N, Schloss MJ, Amatullah H, et al. Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. Nat Med (2019) 25(11):1761–71. doi: 10.1038/s41591-019-0633-x

137. Berger G, Marloye M, Lawler SE. Pharmacological Modulation of the STING Pathway for Cancer Immunotherapy. Trends Med (2019) 25(5):412–27. doi: 10.1016/j.molmed.2019.02.007

138. Saeed A, Ruan X, Guan H, Su J, Ouyang S. Regulation of cGAS-Mediated Immune Responses and Immunotherapy. Adv Sci (Weinh) (2020) 7(6):1902599. doi: 10.1002/ads.201902599

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Liao, Du and Wang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.