Cytosolic sensor STING in mucosal immunity: a master regulator of gut inflammation and carcinogenesis

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Abstract
The stimulator of interferon genes (STING) connects microbial cytosolic sensing with host cell effector functions. STING signaling plays a central role in cyclic dinucleotides (CDNs) and DNA sensing to induce secretion of interferons and pro-inflammatory mediators. Although activated STING signaling favors antimicrobial progress and facilitates mucosal wound healing, its role in mucosal immunity and gut homeostasis is paradoxical, ranging from positive and negative effects within the gut. In our review, we summarize recent advance of STING signaling in gut homeostasis and inflammation, especially focusing on its molecular basis in mucosal immune response. Deep understanding of the regulatory mechanisms of intestinal STING pathway could promote clinical manipulation of this fundamental signaling as a promising immunomodulatory therapy.

Keywords: STING, Mucosal barrier, Intestinal inflammation

Background
Persistent exposure of intestinal mucosa to a variety of microorganisms and bacterial metabolism reflects the biological necessity for a multifaceted, integrated epithelial and immune cell-mediated regulatory system[1]. Disruption of intestinal homeostasis plays an important role in the development of systemic inflammatory response, leading to tissue inflammation and organ injury. Acute and chronic conditions such as inflammatory bowel disease (IBD), sepsis, and gastrointestinal (GI) cancer are associated with the imbalance of gut homeostasis[2]. Abbreviated activation of innate and adaptive immune response could potentially induce the development of severe inflammatory condition in gut.

Stimulation by bacterial-derived pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) provoke intestinal pattern recognition receptors (PPRs), which are involved in the intestinal immune response and inflammation[3]. This research direction recently developed into a novel dimension with cytosolic surveillance systems. The adaptor protein stimulator of interferon genes (STING) is a vital milestone in sensing nucleotide research. STING connects microbial cytosolic sensing with host cell effector functions. Cyclic dinucleotides (CDNs) are important bacterial metabolism and while DNA is presented in most microorganisms, both of which could activate STING signaling. Besides, STING can recognize host self-DNA, including nuclear DNA (nDNA) and mitochondrial DNA (mtDNA), conferring on STING an important role in host immune response[4, 5].

STING discovered by Barber et al. at 2008, is an endoplasmic reticulum (ER) adaptor that regulates intracellular DNA-mediated, type I interferon-dependent innate
immunity [6]. However, the related pathway remains unknown at that moment. In 2013, Chen’s group discovered a new cytosolic DNA sensor cyclic GMP-AMP (cGAMP) synthetase(cGAS), declaring the arrival of “cGAS-STING” era [7, 8]. Since then, numerous studies have investigated that the activation of STING was essential for host defenses against viral and bacterial infections as well as cancer. However, increasing evidences showed that the excessive activation of STING could contribute to various diseases, including autoimmune and inflammatory diseases. Particularly, recent studies demonstrated that STING signaling was associated with intestinal homeostasis, i.e., STING signaling could be beneficial or detrimental to gut barrier in different scenarios. It is therefore necessary to balance the conservation and activation of STING signaling in response to microbial PAMPs and self-DAMPs in gut.

**Activation of STING signaling**

STING is an ER-resident protein in various cell types, including epithelial and endothelial cells, macrophages and dendritic cells (DCs). Activated STING is associated with enhanced secretion of type I interferon (IFN) and inflammatory cytokines in response to PAMPs and DAMPs. In steady state, cytoplasmic DNA degrades quickly through nucleases or endolysosomal compartments. In pathological conditions, self or microbial DNA accumulates in the cytosol, which was recognized by cGAS and its second messenger cGAMP [9]. cGAMP could translocate into adjacent cells via volume regulated anion channels or gap junctions, resulting in the activation of STING in neighboring cells [10, 11].

Upon binding to cGAMP, STING traffics via Golgi apparatus and ER–Golgi intermediate compartment (ERGIC), regulated by the cytoplasmic coat protein complex II and ADP-ribosylation factor (ARF) GTPases [12]. Activated STING subsequently recruits TANK-binding kinase 1 (TBK1), and phosphorylates interferon regulatory factor 3 (IRF3) and nuclear factor-κB (NF-κB). These transcriptional factors are capable to translocate from cytoplasm into nucleus to induce innate immune genes transcription, contributing to the production of type I IFN and inflammatory cytokines (Fig. 1).

STING signaling also plays an important role in autophagy, cell death, and senescence [13, 14]. Recently, Li et al. [15] found that mtDNA-STING pathway could induce autophagy-dependent ferroptotic cell death via lipid peroxidation. Intense efforts are underway to develop both inhibitors and activators of STING, which could be beneficial for the management of autoimmune disease and cancer [16, 17]. Pan et al. [18] identified MSA-2 as a potent STING agonist, and oral MSA-2 exhibited durable STING-dependent antitumor effect.

**Regulation and modification of STING signaling**

Sophisticated regulation of STING signaling is critical to avoid excessive immune response. MicroRNAs were

![Fig. 1] Overview of STING signaling. STING is activated by CDNs produced by bacteria or by cGAS following binding to cytosolic DNA. Activated STING in ER contributes to translocation of STING to Golgi, where interaction with TBK1 happens via the C-terminal tail of STING. Activated TBK1 can enable the recruitment and phosphorylation of IRF3 and NF-κB, which leads to enhanced production of type I interferon and inflammatory cytokines. STING signaling also participates in other cellular process, including autophagy and different types of cell death. CDNs, cyclic dinucleotides; cGAS, cyclic GMP–AMP synthase; ER, endoplasmic reticulum; TBK1, TANK-binding kinase 1; IRF3, interferon regulatory factor 3; NF-κB, nuclear factor-κB.
recently found to regulate STING expression. miR-210 [19], miR24-3p [20] and MiR-576-3p [21] could inhibit STING expression at both translational and protein levels. In contrast, miR29a and miR378b could activate STING signaling [22]. In resting cells, STING binds to the Ca\(^{2+}\) sensor stromal interaction molecule 1 (STIM1) within ER. Once STING binds to the cGAMP, the interaction between STING and ER-resident protein STIM1 was disrupted, initiating STING translocation from ER to Golgi [23]. How STING dimerizes and traffics from ER to ERGIC has been explored recently. ER-associated protein ZDHHC1 is important for innate immune response, and overexpression of ZDHHC1 activated the promoter of INF-\(\beta\). ZDHHC1 was colocalized with STING in ER, and was constitutively associated with the dimerization of STING and recruitment of TBK1 [24].

Post-translational modifications (PTMs) of STING have been extensively investigated recently. S358, Ser366, and Y245 are three phosphorylation sites for STING activation (Table 1) [25, 26]. Conversely, autophagy-related gene (ULK1) induces S366 phosphorylation, contributing to STING degradation and abolishment of IFN and inflammatory cytokines production [27]. The tyrosine-protein phosphatase nonreceptor type 1 and 2, and PPM1A could dephosphorylate STING, respectively [28, 29], leading to degradation of STING.

Besides phosphorylation, other types of PTMs including polyubiquitination, palmitoylation, nitro-alkylation and sumoylation were observed as well. Several types of polyubiquitin modifications such as K11-, K27-, K63- and K48-linked polyubiquitination regulate STING expression level and activity in both steady and stimulated cells. K11-, K27-, K63-associated polyubiquitination was crucial for stabilizing STING and recruiting TBK1 [30–34]; while K48-linked polyubiquitination was associated with STING degradation in a proteasome pathway [35, 36].

 Trafficking of STING from ER to Golgi apparatus is essential for the activation of downstream pathway. STING is palmitoylated at Cys88 and Cys91 at the Golgi apparatus [37]. Treatment of nitro-fatty acids could modifies Cys88 and Cys91 of STING through nitro-alkylation in ER, inhibiting normal palmitoylation [38].

| Type of PTMs | Sites | Enzyme | Consequences | Ref |
|-------------|-------|--------|--------------|-----|
| Phosphorylation | Y245, S358, S366, Y245 | SRC, TBK1, TBK1, ULK1 | dimerization and stability of STING, Recruitment of TBK1, Recruitment of IRF3, Induces degradation of STING | 26, 27, 28 |
| Dephosphorylation | Y245, S358 | PTPN1/2, ULK1 | Degradation by a proteasome pathway, Suppression of STING activity | 29, 30 |
| Ubiquitination | K150 | RNF26, AMFR, TRIM32, MUL1 | Promotes stability of STING, Promotes recruitment of STING, Promotes the interaction of STING with TBK1, Enhances trafficking of STING | 31, 32, 33, 34 |
| K11-linked polyubiquitination | K150 | RNF26 | Promotes stability of STING | 31 |
| K27-linked polyubiquitination | K137/150/224/236 | AMFR, TRIM32, MUL1 | Promotes recruitment of STING, Promotes the interaction of STING with TBK1, Enhances trafficking of STING | 32, 33, 34 |
| K63-linked polyubiquitination | K20/150/224/236 | TRIM32, MUL1 | Promotes the interaction of STING with TBK1, Enhances trafficking of STING | 33, 34 |
| K63-linked polyubiquitination | K224/236/289/338 | MUL1 | Enhances trafficking of STING | 34 |
| K63-linked polyubiquitination | K20/150/224/236 | TRIM32, MUL1 | Promotes the interaction of STING with TBK1, Enhances trafficking of STING | 33, 34 |
| K63-linked polyubiquitination | K150 | TRIM32, MUL1 | Promotes recruitment of TBK1 and induction of INF-\(\beta\), Enhances trafficking of STING | 35, 36 |
| K48-linked polyubiquitination | K275 | TRIM30, RNF5 | Proteasomal degradation of STING, Proteasomal degradation of STING | 36, 37 |
| Palmitoylation | C88/91 | DHHC | Enhances trafficking of STING | 38 |
| Nitro-alkylation | C88/91 | N.D. | Inhibits normal palmitoylation process | 39 |
| Carbonylation | C88 | GPX4 | Inhibition of STING trafficking from the ER to the Golgi | 40 |
| Sumoylation | K338 | TRIM38 | Promotes oligomerization and stability of STING | 41 |
| Desumoylation | K388 | SENP2 | Lysosomal degradation of STING | 41 |
| Oxidation | C147 | ROS | Inhibition of STING polymerization | 42 |
Additionally, STING was recently showed to be carbonylated by lipid peroxidation, and STING carbonylation inhibited STING palmitoylation and subsequent activation [39]. Sumoylation plays an important role in protein stability. Hu et al. [40] showed that sumoylated STING following DNA stimulation promoted oligomerization and prevented its degradation [40]. Additionally, Reese’s group recently demonstrated that reactive oxygen species could suppress IFN response by oxidizing STING, indicating that redox modification also plays an important role in STING modification [41].

**STING signaling in gut homeostasis**
Persistent exposure of intestinal mucosa to tremendous microorganisms and their metabolites reflects the biological necessity for a multilevel, integrated epithelial and immune cell-mediated regulatory system. Impaired mucosal barrier and disruption of intestinal homeostasis lead to bacterial translocation and mucosal inflammatory response. Recent studies indicated that PAMPs and DAMPs are involved in intestinal STING activation that help to shape gut homeostasis.

**STING signaling in enteropathogenic bacterial infections**
Infectious diarrhea caused by enteropathogenic bacteria is a major cause of morbidity and mortality worldwide [42]. Innate immunity plays a crucial role in preventing enteropathogenic bacterial infections. STING signaling recently provided crucial insights into antimicrobial and immunomodulatory therapeutics against pathogen. *Listeria monocytogenes* is a gram positive facultative intracellular bacterium, and type I IFN is essential for host defense against *Listeria* disease. Released c-di-AMP into host cytoplasm is dependent on multidrug efflux pumps (MDRs) that induces host cytosolic surveillance pathway in murine cells [43]. However, Hansen et al. [44] investigated that in human macrophages, *Listeria* DNA rather than c-di-AMP induces type I IFN response that depends on cGAS-STING pathway. Additionally, they reported that *Listeria* DNA-induced IFNβ expression is associated with bacteriolysis in human macrophage cytosol. Further studies are necessary to identify the interaction between innate and protective immunity following *Listeria* infection.

Unlike *Listeria, Shigella flexneri*, a causative agent of bacillary dysentery, was found to limit STING signaling. Two Shigella type 3 secretion system (T3SS) effector proteins (IpaA) and VirA) were capable to disrupt immune response [45]. Dobb et al. [46] found that *Shigella* IpaA could suppress STING signaling and type I IFN response through inhibiting its translocation from ER to ERGIC. VirA could cause STING retention in ERGIC, but failed to inhibit type I IFN. Moreover, Dong et al. [47] found that inactivation of Rab1 by VirA caused increased bacterial burden in cytoplasm by suppressing autophagy-mediated immune response.

*Salmonella* is another intracellular pathogen that causes severe gastrointestinal and systemic infection. STING-deficient mice exhibited increased mortality rate compared to WT counterparts following oral administration of *Salmonella typhimurium* [48]. Park et al. [49] recently demonstrated that STING-IRF1-dependent signaling in DCs was able to drive TH17 polarization in response to evaded entero-pathogen (e.g., *Salmonella*) in gut.

**STING is associated with sepsis-induced intestinal injury**
Gut has been suggested as the ‘driver’ of sepsis and organ injury [50]. Gut epithelium, immune system and microbiome were significantly disrupted during sepsis [51]. Our recent study found that STING was remarkably activated in the gut of sepsis patients, which was associated with exacerbated historical injury and elevated intestinal epithelial cell apoptosis [52]. Our findings suggest a critical involvement of STING-induced excessive inflammation and intestinal epithelial cells (IECs) apoptosis sensing by CDNs and host DNA during sepsis, leading to intestinal barrier damage, increased intestinal permeability [52]. Zeng et al. [53] also demonstrated that STING depletion improved survival in both lethal endotoxemia and polymicrobial sepsis model, which was associated with leukocyte infiltration and tissue destruction.

STING was originally discovered as a cytosolic nucleic-acid sensor dependent on cGAS, a DNA-binding protein. Emerging evidence has demonstrated that circulating DNA derived from injured host cells or invading pathogens was significantly increased in sepsis patients, and was associated with adverse outcomes [54, 55]. However, unlike STING−/−, cGAS depletion failed to prevent against sepsis-induced mortality and tissue injury, implying that other DNA sensors may play a more important role during sepsis.

Zhang et al. [56] identify an alternative STING pathway in organ failure. STING-mediated GSDMD (a pore-forming protein) cleavage by caspase1/caspase11 or caspase8 induces tissue factor F3 release and lethal coagulation independent of classical downstream of STING signaling. Li et al. [57] recently investigated that STING leads to lipopolysaccharide-induced tissue dysfunction, inflammation, apoptosis and pyroptosis by activating NLRP3 (NOD-like receptor family, pyrin domain containing 3) signaling (Fig. 2). Therefore, both canonical and alternative STING signaling are involved in the development of sepsis. However, the specific mechanism that how STING is precisely activated in infected cells or septic gut remains largely unknown.
STING signaling in IBD-associated intestinal disorder

STING has been suggested as a negative regulator in various autoinflammatory diseases, such as systemic lupus erythematosus, and rheumatoid arthritis [58]. However, the role and potential mechanism of STING signaling in IBD remain largely unknown.

IBD, including Crohn’s disease (CD) and ulcerative colitis, is a chronic and relapsing immune disorder. Recent studies suggested that DAMPs released from extensively inflamed mucosa act as a ‘motor’ in inducing and maintaining intestinal inflammation. DAMPs are responsible for mucosal inflammatory insults in both human and animal model. Our recent study discovered that mitochondrial DAMPs (mtDNA) released from gut mucosa could induce intestinal inflammatory response dependent on STING signaling, and the induction of STING signaling in intestine of active CD patients supports a potential pathogenic role of STING in IBD [3, 52].

Canesso et al. [48] observed that STING knockout mice showed a higher susceptibility to T-cell-induced and DSS-induced colitis compared to WT littermates, suggesting a protective effect of STING pathway in gut homeostasis. Barber’s group confirmed that STING-deficient mice were prone to polyp formation and intestinal inflammation in response to DSS stimulation [59]. They suggested that STING signaling was crucial for wound healing and antimicrobial processes by preventing microbes invading into lamina propria where they could induce excessive inflammatory response. These studies consistently demonstrated an association between STING deficiency and aggravated intestinal inflammation.

It is plausible that treatment of STING agonist can improve DSS-induced colitis. However, Martin et al. [60] recently demonstrated that STING agonist deteriorated DSS-induced colonic injury, significant weight loss and colonic shortening. Ahn et al. also found that STING deficiency could prevent colitis due to impaired IL-10 production [59]. IL-10 is an anti-inflammatory cytokine that requires the activation of transcription factors IRF3 and NFκB [61]. Therefore, it is reasonable that STING can induce the secretion of IL-10. Without STING-dependent IL-10 secretion, increased inflammatory mediators triggered by STING could induce a higher inflammatory state. Meanwhile, Aden et al. [62] demonstrated that activated STING signaling in intestinal epithelial cell induces a strong TNF and interferon-stimulated genes response, which leads to excessive ileal inflammation and widespread epithelial cell necroptosis.

In summary, STING signaling may play a paradoxical role in gut homeostasis during the development of IBD. STING signaling determines the outcomes of IBD depending on types of immune cells involved. Gut mucosal immune response is regulated by several innate receptors beyond STING. DSS-induced gut inflammation may enable microbes access to the lamina propria where they could activate STING-independent inflammatory signaling, such as Toll-like receptors and NOD-like receptors [3].

cGAS is a fundamental upstream protein of STING. Interestingly, cGAS may play a different role compared to STING in the development of IBD. cGAS-deficient mice showed modest inflammatory response and polyp formation by DSS treatment [59], and cGAS inhibitor remarkably alleviated the clinical signs of colitis in mice [63]. It is still unclear why cGAS-deficient mice exhibited moderate intestinal inflammation following DSS challenge compared with STING-deficient mice. It is possible that microbiota-derived CDNs play a more crucial role in the development of colitis than microbial or self-free cytosolic DNA species. Therefore, further
studies need to compare the pathogenic effect between bacteria-derived CDNs and genomic DNA in the development of colitis.

**STING signaling and cancer**  
**Anti-tumorigenesis effect of STING**  
Recent advance has suggested an important role of STING signaling in the development of GI cancer. Increased tumor load was observed in STING knockout mice following azoxymethane/dextran sodium sulfate (AOM/DSS) treatment that can cause colitis-associated cancer (CAC). The deficiency of STING was associated with increased inflammatory response and significant dysplasia in colorectal tissues.

STING-dependent signaling is capable to induce IL-1 and IL-18 production. Decreased expression of IL-1β and pre-caspase-1 were observed in colon tissues of STING knockout mice [59]. Consistently, IL-18 and IL-22BP expression were found decreased in the colon tumor of AOM/DSS-treated STING knockout mice compared to WT mice [64]. It is possible that cell repair factors (IL-1β, IL-18) activated by STING signaling promotes intestinal wound healing, which can prevent microbiome translocating into lamina propria where they can activate inflammatory pathway (Fig. 3). When natural wound healing was interrupted, persistent inflammation would disrupt the intestinal microbial composition, contributing to further inflammatory response, DNA damage and cancer development [65, 66]. In tumors and cancer cell lines, STING signaling is frequently silenced or mutated, indicating its role in limiting tumor growth. Decreased STING expression was positively associated with tumor invasion depth, lymph node metastasis, and reduced patients’ survival in gastric cancer patients [67]. Nevertheless, no mutation was showed in genome encoding cGAS-STING signaling through gene sequence analysis and the suppression may be attributed to epigenetic modification, such as hypermethylation. Collectively, suppression of STING function is a crucial obligation for tumorigenic process.

Adaptive T cell response is fundamental for controlling and eradicating tumor cells. DCs and IFN are crucial to induce adaptive T cell response [68]. It is suggested that DCs can engulf necrotic tumors cell, and the tumor-derived DNA activates STING signaling and enhances the production of type I IFN in DCs [69], which acts in an autocrine or paracrine pattern and activates the generation of additional proteins within the DCs to induce cross-presentation and T cell activation. Early Colorectal cancer patients showed higher STING expression with increased intratumoral CD8+ T cell infiltration and less frequent lymphovascular invasion. Moreover, intratumoral STING treatment was suggested to inhibit colon cancer progression through enhanced CD8+ T cells [70]. Other PRRs, including TLR and RIG-like receptors (RLRs), also activate type I IFN response. However, Woo et al. [71] showed that STING-IRF3 pathway-dependent type I IFN, rather than other IFN-associated signaling, in DCs is required for endogenous antitumor CD8+ T cell response. Tumor-derived DNA captured by cGAS in DCs as well as tumor cells themselves in tumor microenvironment (TME) is the primary driving force to activate STING signaling to induce the production of type I IFN and the tumor-specific CD8+ T cell priming (Fig. 4). Additionally, recent studies also suggested that STING activation in TME can suppress the function of immunosuppressive cells (regulatory T cells and MDSCs), and induce the activation of NK cells, which could promote destruction of tumor cells [72]. The important role of STING signaling in triggering anti-tumor T responses has inspired interests in the development of STING agonists for cancer therapy. Several studies suggested that CDNs that bind human STING exhibited antitumor effect in animal studies [73]. STING agonists were suggested to be effective against tumors that were resistant to programmed cell death protein 1 (PD1) blockade [74]. Chin et al.[75] recently identified a non-nucleotide, small-molecule STING agonist, termed SR-717, that promoted the activation of CD8+ T, NK cells, and DCs in; and facilitated antigen cross-priming. Additionally, SR-717 also induced the expression PD-L1 in a STING dependent manner [75].

**The protumor effect of STING signaling**  
Recent evidence suggested that STING pathway may play an important role in malignant transformation mainly by activating immune suppressive tumor microenvironment and inducing tumor metastasis. Immune suppressive landscape is indicated during chronic activation of STING
pathway. The immune checkpoint indoleamine 2,3-dioxygenase (IDO) is marker of immune suppressive TME. Decreased IDO was detected in STING-KO mice in TME of lung cancer model [76]. Activation of STING signaling is also associated with increased expression of CCR2 in colon cancer [77]. Elevated expression of CCR2 in MDSCs induced the aggregation of tumor-promoting monocytes. In addition, increasing evidence demonstrated that activated STING in T cells could damage adaptive immune system and accelerate tumorigenesis [78]. However, potential mechanisms of STING in immune suppressive environment remains largely unknown, further studies are needed to identify the relationship between STING and TME.

STING was recently suggested to induce tumor metastasis. Activation of STING signaling was associated with increased inflammatory response and upregulation of NFκB pathway, which contribute to epithelial-to-mesenchymal transition and metastasis [79]. Chen et al. [80] demonstrated that STING was activated in astrocytes and subsequently induced secretion of inflammatory cytokines, leading to brain metastasis of lung cancer and breast cancer. Potential relationship between STING and cancer metastasis remains unknown. One possible mechanisms may be related to the degree of STING levels. Gulen et al. [81] recently indicated that magnitude of STING signaling determined the activation of apoptotic programs in macrophages and T lymphocytes, indicating that regulation of STING levels was associated with distinct downstream effector programs. Our recent studies also showed that degree of STING activation is associated with disease outcomes [82]. Further investigation was needed to uncover the molecular context by which activated STING facilitates tumor metastasis.

The diet, gut microbiota, and STING signaling
The contribution of diet to regulating the microbiota and its important role in orchestrating the host–microbiota crosstalk has been well-recognized [83]. Nutrients can directly interact with microorganisms to promote or inhibit their growth, and dietary interventions could trigger structural and functional alterations in the gut bacteria [83]. To our knowledge, there are no studies to investigate the effects of diet on the intestinal mucosal barrier via regulating STING signaling. STING play an important role in regulating the composition of gut microbiome. Canesso et al. [48] showed that significant differences in relative abundance of bacteria populations between STING−/− and WT mice. There was a greater fecal output in the Proteobacteria and a reduction in the Actinobacteria phylum in the feces from STING−/− mice. Additionally, recent evidence suggests that high-fat diet is associated with activation of STING signaling. Therefore, we consider that diet may modulate gut microbiota through regulating STING signaling, and further studies are need to clarify the potential mechanisms.

Delivery systems of STING agonist
STING agonists have also been suggested to be experimentally useful as adjuvants in anticancer vaccine studies [69].
However, excessive expression of STING in T lymphocytes contribute to T-cell apoptosis, a phenomenon that appeared cell specific as DCs or macrophages did not show such sensitivity [84]. Hence, combination of STING agonists and effective adjuvant/antigen delivery system plays an important role in cancer vaccines, which could specifically target immune cells, including DCs, macrophages and NK cells [85]. Liposomes, polymers, and hydrogels have been suggested efficiently to deliver STING agonist. Koshy et al. [86] investigated that cationic liposomes with polyethylene glycol were used to encapsulate cGAMP to facilitate its cytosolic delivery, leading to antitumor activity. Moreover, Cheng et al. [87] demonstrated that liposomal nanoparticle-delivered cGAMP directed both mouse and human macrophages; increased MHC and costimulatory molecule expression; and enhance T cell infiltration.

Multifunctional polymers are also effective tools to deliver STING agonist. Gao’s group reported a synthetic polymeric nanoparticle, PC7A nanoparticles, which generated a strong cytotoxic T-cell response dependent on STING signaling [88]. Similarly, Zhou et al. developed an engineering polymeric prodrug nanoplatform for vaccination immunotherapy of cancer, which dramatically promoted DC maturation through activating STING signaling [89]. Recently, Lu et al. [90] developed PLGA microparticles for long-term, pulsatile release of STING agonist for cancer immunotherapy. Moreover, other polymer (dextran microparticles) was suggested to transport STING agonist and realize antitumor effect [91, 92].

Different from liposomes and polymer nanoparticles, the advantages of hydrogels as carriers are the local and controlled release of STING agonist, leading to recruitment and activation of immune cells. A recent study developed a novel biomaterial called ‘STINGel’, which was an injectable peptide hydrogel that localized and provided control release of CDN delivery [93]. STINGel improves survival in a challenging murine oral cancer model. Additionally, Cui’s group recently designed a self-assemble hydrogel that can locally deliver STING agonists to activate DCs and NK cells, contributing to long-term immune memory and systemic immune surveillance, thereby reducing tumor immunosuppression and enhancing the efficacy of a wide range of cancer therapies [94]. However, none of these delivery systems have been used in clinic. Additionally, excessive activation of STING signaling could induce systemic inflammation and a cytokine storm. Thus, greater sight into the mechanism could drive us to develop more specific agonist and achieved safe, personalized, and valid therapies.

**Type I IFN in autoimmune diseases and cancer**

Type I IFN (mainly IFN-α and IFN-β) are the main effectors of STING pathway-dependent modulation of innate immunity. Type I IFN pathway is broadly implicated in autoimmune diseases and cancer [95]. Type I IFN is activated in patients with several systemic autoimmune diseases, which seems to be of major importance in the disease process. Both of IFN-α and IFN-β could contribute to systemic lupus erythematosus (SLE) pathogenesis, and blockade of IFNAR provides effective therapy for systemic autoimmune disease [96]. Moreover, type I IFN are increasingly recognized for their role in regulating anti-tumour immune responses. IFN-α/β can directly target tumor cells through inducing apoptosis and growth arrest [97]. Additionally, Targeting type I IFN to tumor microenvironment promotes anti-tumor activity through host adaptive immunity that is T-cell dependent [97]. Several studies demonstrated that the intra-tumoural expression levels of type I IFN or of IFN-stimulated genes correlate with favourable disease outcome in several cohorts of cancer patients [98]. Therefore, therapies designed to increase the intra-tumoural concentration of type I IFN can have antineoplastic effects following the induction of anticancer immune responses. Although type I IFN signaling is required to trigger anti-tumor immunity, emerging evidence indicates that chronic activation of type I IFN pathway may be involved in mediating resistance to different cancer treatments [98]. Therefore, Strategies able to temporarily block IFN-signaling, preferably in cancer cells only, could be useful to limit chronic exposure to IFN and restore responsiveness to treatment.

**Conclusions**

It has been clear that STING plays an important role in intestinal mucosal immunity. The effect and mechanism of STING signaling varies depending on different scenarios. Emerging evidence has showed that activation of STING signaling enhance anti-cancer immune response, and STING agonists have been suggested as promising anti-tumor therapy, including target therapy and immunotherapy. It is worth noting that STING as a vital modulation of inflammation and IFN response, could instigate tumor development and metastasis. Additionally, degree of STING molecule is associated with cancer outcome. Therefore, the tumor status and therapeutic windows should be carefully evaluated before using STING agonists or antagonists. Further studies are expected to help clinician select appropriate STING modulators according to specific condition.

**Abbreviations**

STING: Stimulator of interferon genes; CDNs: Cyclic dinucleotides; IBD: Inflammatory bowel disease; GI: Gastrointestinal; PAMPs: Pathogen-associated molecular patterns; DAMPs: Damage-associated molecular patterns; PRRs: Pattern recognition receptors; mtDNA: Mitochondrial DNA; ER: Endoplasmic reticulum; DCs: Dendritic cells; IRF3: Interferon regulatory
factor 3; NF-xB: Nuclear factor-xB; P'TMs: Post-translational modifications; CAC: Colitis-associated cancer; PDL1: Programmed cell death protein 1

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