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REVIEW

The emerging role of STING-dependent signaling on cell death

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Abstract
STING is a newly identified adaptor protein for sensing cytosolic nucleic acid. It is well established that STING plays a crucial role in innate immune response via inducing production of type I IFN. Emerging evidence suggests that the activation of STING-dependent signaling is also implicated in the process of cell death, such as apoptosis, pyroptosis, necroptosis, and autophagy. Of note, the pro-death outcome is even predominant in certain cell types, like lymphocytes, myeloid cells, and hepatocytes. Given that STING agonists are being tested for enhancing antitumor immune responses, it is necessary to fully understand the outcome of STING activation. The anti-microorganism response mediated by STING has been well described; therefore, we focus on the role of STING-dependent signaling on cell death in this review.

Keywords STING · IRF3 · Apoptosis · Pyroptosis · Necroptosis · Autophagy

Introduction

STING (stimulator of interferon genes, encoded by *TMEM173*) is a cytosolic DNA sensor and plays an essential role in innate immune responses [1]. The identification of STING-dependent signaling pathway represented a milestone for nucleotide sensing research. Beyond resisting invading pathogens, recent findings suggested that STING also participated in the process of various autoinflammatory diseases and even cancer [2].

STING is widely expressed in endothelial and epithelial cells, especially in hematopoietic cells, such as T lymphocytes, and myeloid cells [3]. Cytosolic DNA species involves exogenous DNA from the invading pathogens and self-DNA leaked from the nucleus or mitochondria [4, 5]. When sensing cytosolic DNA species, cyclic GMP-AMP synthase (cGAS) catalyzes the formation of a type of cyclic dinucleotide (CDN) termed cGAMP (cyclic GMP-AMP) [6]. cGAMP further activates STING in the endoplasmic reticulum (ER). Then, activated STING migrates to perinuclear Golgi accompanied the recruitment of TANK-binding kinase 1 (TBK1). The STING-TBK1 complex phosphorylates interferon regulatory factor 3 (IRF3) and nuclear factor-κB (NF-κB). These transcription factors then traffic into the nucleus for inducing type I IFN-related gene transcription [7]. In certain cases, STING might be directly activated by CDNs derived from bacteria, such as cyclic di-AMP (c-di-AMP) secreted by *Listeria monocytogenes* [8, 9]. The above description presents the full process of innate immunity from sensing the invading pathogens or dying cells to producing inflammatory cytokines.

Self-DNA from tumors is also reported to be capable of activating STING pathway, which further enhances antitumor immune response [10, 11]. This finding contributed to the development of tumor immunotherapy using STING agonists. As the earliest applied STING agonist, DMXAA (5,6-dimethylxanthenone-4 acetic acid) presented promising antitumor effects in mouse models, but failed in clinical trials because of the different structure of STING between mouse and human [12]. Current studies mainly focused on the nucleotide STING agonist termed CDNs. CDNs are small-molecule second messengers that activate STING directly. It contains c-di-AMP, c-di-GMP derived from bacteria, and cGAMP produced by cGAS. Intratumoral injection of CDNs has shown remarkable efficacy in mouse xenograft models [10, 13, 14]. It was also reported that CDNs had synergistic effects with chemotherapy, radiotherapy, and immunotherapy [15]. At present, three phase I clinical trials of intratumoral injected CDNs alone or combination with anti-PD-1 therapy

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are under evaluated (NCT02675439, NCT03172936, NCT03010176) [16]. Simultaneously, to improve the intracellular delivery efficiency and overcome the clinical limitation of intratumoral injection, various nanoparticles were applied, such as liposomal nanoparticles, poly (beta-amino ester) (PBAE) nanoparticles, PEGylated lipid nanoparticles, ultra–pH-sensitive nanoparticles, and cationic silica nanoparticles (CSiNPs) [17–21]. In addition, some novel non-nucleotide STING agonists are also under investigation [22].

Although STING signaling pathway is well characterized for generating the innate immune response, emerging evidence has uncovered that STING activation was also involved in non-inflammatory responses, such as autophagy, cross-presentation, and even cell death [23–25]. Given that STING agonists are considered a promising sort of immunotherapy adjuvant, it is necessary to fully understand the outcome of STING activation. In this review, we will focus on the role of STING-dependent signaling on cell death (Table 1).

STING signaling and apoptosis

STING signaling was first reported to be involved in apoptosis in 2014 [38, 39]. Rongvaux et al. and White et al. proved independently that during apoptosis, Bak/Bax induced the leakage of mitochondrial DNA (mtDNA), which was sensed by cGAS/STING pathway and further initiated IFN production. Of note, they noticed that apoptotic caspases could suppress this response and subsequently silencing the mtDNA-mediated immune response during apoptosis [38, 39]. Although these two studies clarified the interaction between STING signaling and apoptosis, the function of STING signaling was still limited in pro-inflammatory response. Recent studies have proved that STING-dependent signaling could promote apoptosis directly in various types of cells, especially in lymphocyte.

STING signaling promotes apoptosis of lymphocytes

Tang et al. first reported that STING agonist was capable of triggering apoptosis both in normal and malignant B cells [26]. In vivo tests clarified that STING agonists might be a promising therapeutic agent for B cell malignancies. In addition, this study further analyzed the reason why STING agonist induced apoptosis in B cells, while triggered production of IFNs in other types of cells [26]. They found that STING was degraded more slowly in B cells, causing the prolonged activation of STING signaling, and then might engage mitochondria-mediated apoptosis. With respect to T cells, Larkin and colleagues elucidated that activation of STING not only provoked production of IFN but also triggered cell death [40]. These results were confirmed by another study

Table 1 Examples of cell death induced by STING-dependent signaling in individual components

Model and Cell	Cell death type	Cell death parameters	Reference
cGAMP-induced STING activation; normal and malignant B cells	Apoptosis	Increased cleaved caspase-3,7,9	Tang et al. 2016 [26]
CMA or DMXAA-induced STING activation; normal and malignant T cells	Apoptosis	Increased two BH-3 only proteins Noxa and Puma	Gulen et al. 2017 [24]
HTLV-1 virus infection; monocytes	Apoptosis	Increased IRF3-Bax complex	Sze et al. 2013 [27]
M. bovis infection; macrophage	Apoptosis	Increased IRF3-Bax complex, caspase-8/3	Cui et al. 2016 [28]
Ethanol-induced alcoholic liver disease; hepatocyte	Apoptosis	Increased ER stress	Petrasek et al. 2013 [29]
CCl_4-induced liver fibrosis; hepatocyte	Apoptosis	Increased ER stress	Iracheta-Vellve et al. 2016 [30]
High-fat diet-induced nonalcoholic fatty liver disease; hepatocyte	Apoptosis	Increase cleaved caspase-3	Qiao et al. 2018 [31]
Chlamydia trachomatis infection; bone marrow derived macrophages	Pyroptosis	Increased AIM2 inflammasome	Webster et al. 2017 [32]
Francisella infection; bone marrow derived macrophages	Pyroptosis	Increased IRF1, guanylate-binding proteins, AIM2 inflammasome	Man et al. 2015 [33]
Lipofected DNA-induced STING activation; myeloid cells	Pyroptosis	Increased lysosomal cell death, NLRP3-inflammasome	Gaidt et al. 2017 [34]
MHV68 virus infection; fibrosarcoma L929 cell line	Necroptosis	Increased TNF	Schock et al. 2017 [35]
DNA transfection-induced STING activation; bone marrow derived macrophages	Necroptosis	Increased type I IFN and TNF, activated RIPK3	Brault et al. 2018 [36]
STING transfection; MCF-7 cells	Autophagy	Increased p62, NDP52	Bhatelia et al. 2017 [37]

recently [24]. Gulen et al. elucidated that T cells exhibit a proapoptotic response rather than the production of IFNs under the stimulation of STING agonists [24]. Mechanistically, they found that the expression level of STING in T cells was higher than other cell types, so T cells exhibited an intensified STING response. The intensified STING response was associated with the induction of two BH3-only proteins, Noxa and Puma. Additionally, the proapoptotic STING response also existed in malignant T cells, providing a potential therapeutic target for T cell malignancies [24].

Taken together, it seems that the intensity of STING response determines the outcome of STING signaling activation. The intensified STING response tends to trigger apoptosis, while the non-intensified STING response tends to trigger production of type I IFN. As apoptosis is also considered as a way for the host to resist intracellular microorganism [41, 42], we speculate that at the early stage of infection or stimulated by a small number of microorganisms, activated STING signaling tends to induce the production of IFNs. Instead, at the chronic stage of infection or stimulated by a large number of microorganisms, activated STING signaling tends to trigger apoptosis. Of note, STING-mediated apoptosis exists in normal lymphocyte. It sounds the alarm for the therapeutic applications of STING agonists in treating cancers.

STING signaling promotes apoptosis of myeloid cells

Besides lymphocytes, the proapoptotic effect of STING was elucidated in myeloid cells. Sze et al. demonstrated that when human T cell leukemia virus type 1 (HTLV-1) invaded monocytes, cytosolic reverse transcription intermediates (RTI) could induce the production of IRF3-Bax complex through activating STING [27]. The IRF3-Bax complex further evoked the mitochondria-mediated apoptosis. Similarly, Cui et al. found that during *Mycobacterium bovis* (*M. bovis*) infection, activated STING-TBK1-IRF3 pathway engaged apoptosis of macrophages by interacting with Bax and caspase-8/caspase-3 [28].

Recently, Chattopadhyay et al. have uncovered the mechanism of IRF3-mediated pathway of apoptosis [43]. Unlike activated by phosphorylation as a transcription factor, IRF-3 was activated by ubiquitination in the proapoptotic pathway. Two specific Lys residues, located in 193 and 313, of IRF3 could be polyubiquitinated by LUBAC (the linear polyubiquitinating enzyme complex). This modification triggered IRF-3 to connect with Bax and finally induced apoptosis. Although this study reported that the proapoptotic signaling complex was assembled in IPS1 (mitochondrial antiviral-signaling protein), it appears plausible to extrapolate these results to STING. Interestingly, a recent study has successfully observed the process of mtDNA efflux during BAK/BAX-driven apoptosis by live-cell lattice light-sheet microscopy [44]. These leaked mtDNA subsequently activated STING-mediated inflammatory response.

Based on these results mentioned above, we speculate that there might be a proapoptotic positive feedback loop formed by STING, IRF-3, and mtDNA. STING/TBK1 activated IRF-3 by ubiquitination; ubiquitinated IRF-3 links to BAX, inducing mitochondrial apoptosis and mtDNA leakage, which in turn activates STING. These results provided an emerging cell death pathway to resist viral or bacterial infections in myeloid cells.

STING signaling promotes apoptosis of hepatocytes

Szabo and colleagues showed for the first time that STING/TBK1/IRF3 pathway played a crucial pathogenic role in liver disease by triggering hepatocyte apoptosis [29, 30]. Under the stimulation of ethanol or CCl_4, STING/TBK1/IRF3 mediated interaction between ER stress and apoptosis in hepatocytes, determining the early stage of alcoholic liver disease (ALD) and liver fibrosis. Recently, another group reported a similar phenomenon in nonalcoholic fatty liver disease (NAFLD) [31]. They found that high-fat diet could activate STING-IRF3, which further promoted both inflammation and apoptosis signaling pathway of hepatocytes. Collectively, the crosstalk between ER stress and apoptosis mediated by STING-dependent signaling plays an essential role in the development of liver disease. This provides a probable therapeutic target for early intervention programs for liver injury.

In summary, the outcome of STING activation varies in distinct cell types. The proapoptotic effect seems to be more prominent in lymphocytes, myeloid cells, and hepatocytes. Mechanistically, as shown in Fig. 1, three major pathways are implicated in STING-mediated apoptosis: 1. Activated STING recruits LUBAC, which triggers IRF3 by ubiquitination. Then ubiquitinated IRF3 binds Bax, contributing to mitochondrial apoptosis. 2. IRF3 stimulated by STING could alternatively promote the transcription of Noxa and Puma; these BH3-only proteins further interact with Bax/Bak to induce cell death. 3. Activated STING/IRF3 recruits FADD and caspase-8 and subsequently triggers downstream caspases.

STING signaling and pyroptosis

Pyroptosis is a form of lytic cell death programmed by the inflammatory caspase and plays a fundamental role in antimicrobial response [45]. It is mediated by caspase-1 canonical inflammasomes or caspase-11 non-canonical inflammasomes. A series of studies have uncovered the interaction between pyroptosis and STING-dependent signaling [32]. Webster and colleagues reported that the metabolite of intracellular *Chlamydia trachomatis*, cyclic di-AMP was detected directly by STING, which further activated both canonical and non-

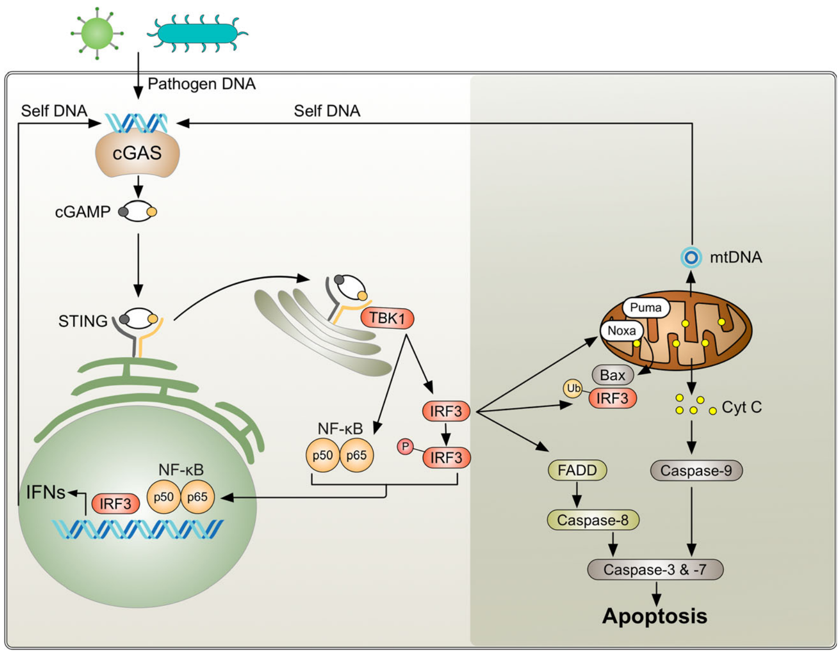

Fig. 1 The dichotomous roles of STING-dependent signaling. Exogenous DNA or self-DNA is sensed by cyclic GMP-AMP synthase (cGAS), which catalyzes the production of a second message-termed cyclic GMP-AMP (cGAMP). cGAMP further activates STING in the endoplasmic reticulum (ER). Then, activated STING migrates to perinuclear Golgi accompanied the recruitment of TANK-binding kinase 1 (TBK1). The STING-TBK1 complex phosphorylates interferon regulatory factor 3 (IRF3) and nuclear factor- κB (NF-κB), leading to the induction of type I IFN. On the other hand, activated STING/TBK1 complex might trigger IRF3 by ubiquitination. Ubiquitinated IRF3 binds Bax, which contributes to the release of Cyt C and activation of Caspase-9/-3/-7; finally triggers mitochondrial apoptosis. IRF3 stimulated by STING might alternatively promote the transcription of Noxa and Puma; these BH3-only proteins further interact with Bax/Bak to induce cell death. Activated STING/IRF3 could also recruit FADD and caspase-8 and subsequently triggers downstream caspases

canonical inflammasomes [32]. Mechanistically, Man et al. suggested that the transcription factor IRF1 mediated the STING-driven pyroptosis [33]. During infection of *Francisella tularensis* subspecies *novicida (F. novicida)* in macrophages, cGAS/STING pathway was activated; elevated production of type I IFN-induced expression of IRF1, allowing the induction of guanylate-binding proteins (GBPs). GBPs contributed to the leakage of bacterial DNA and finally activated the absent in melanoma (AIM2) inflammasome [33]. In addition, it was documented in human myeloid cells, STING-dependent NLRP3 activation functioned as the fundamental mediator in cell pyroptosis. Different from the classical signaling pathway that involves TBK1 and IRF3, activated STING could alternatively migrate directly to lysosomes, resulting in their disruption and subsequently trigger lysosomal cell death (LCD) [34]. LCD further initiated K^+ efflux and finally engaged NLRP3-mediated pyroptosis.

However, recent studies have drawn different conclusions about the relationship between STING signaling and pyroptosis [46, 47]. It is well established that cytosolic DNA is sensed by cGAS and AIM2, leading to type I IFN responses and inflammasome, respectively. Corrales et al. and Banerjee et al. reported subsequently that activation of the AIM2 inflammasome antagonized the STING pathway [46, 47]. Mechanistically, gasdermin D triggered by the AIM2 inflammasome initiated K^+ efflux through membrane pores, which was sufficient to restrain cGAS/STING-dependent type I IFN response [47]. These findings provided a probable IFN regulatory module during pyroptosis. Therefore, more studies are warranted for the precise role of STING-dependent signaling in pyroptosis.

STING signaling and necroptosis

Necroptosis is a programmed form of cell death characterized by early loss of plasma membrane integrity, cell swelling, and leakage of cytosolic contents into the intercellular space [42]. Unlike other types of necrosis, necroptosis is a tightly regulated process, which is governed by RIP1/RIP3/MLKL signaling pathway. A series of studies implied that STING signaling might function as a mediator in the process of necroptosis [35, 36, 48]. Schock et al. elucidated that murine gammaherpesvirus-68 (MHV68) were capable of triggering cell necroptosis through STING pathway in a TNF-dependent fashion [35]. Another group drew a similar conclusion in bone marrow-derived macrophages [36]. They found that introduction of cytosolic DNA could activate RIPK3 and necroptosis mediated by cGAS/STING-driven production of type I IFN and TNF. Notably, Chen et al. revealed a positive feedback loop between necroptosis and STING [48]. They found that during necroptosis, PUMA was transcriptionally activated, mediated by RIP3/MLKL pathway. Activated PUMA resulted in the leakage of mtDNA; then enhanced the phosphorylation of RIP3 and MLKL in a STING-dependent manner, contributing to signal amplification of necroptosis in a positive feedback cycle.

STING signaling and autophagy

Autophagy is a cellular catalytic process that disassembles unnecessary or dysfunctional components [49]. It assists in maintaining cell homeostasis through the orderly degradation and recycling of cellular constituents [50]. Autophagy participates in various biological processes. Beyond nutrient starvation, autophagy is also reported to be implicated in animal development, cell differentiation, innate immune response, cancer, etc. [51–54]. Although it remains unclear whether autophagy is the origin of death or a survival mechanism to prevent it, autophagy is intimately associated with cell death [55, 56].

Recently, there have been compelling suggestions that STING-dependent signaling functions in the process of autophagy [25, 37, 57]. Bhatelia et al. demonstrated that STING could inhibit the fusion of autophagosome with lysosome, which led to the accumulation of mitochondrial ROS and finally cell death in breast cancer cells [37]. In contrast, more studies showed the positive effect of STING signaling on autophagy [25, 57]. Liang et al. suggested that cGAMP induced autophagy in a STING-dependent manner, allowing degradation of microbial DNA and well-balanced immune responses [57]. These results were confirmed by another group; Moretti and colleagues revealed that once sensing c-di-AMP derived from Gram-positive bacteria, STING subsequently triggered ER stress, mTOR inactivation, ER-phagy, and eventually curtailed cell death [25, 58]. Autophagy triggered by STING not only maintains homeostasis to prevent cell death but also controls the infection of microbial. Watson et al. and Liu et al. proved respectively that STING interacted with LC3 to trigger autophagy, that contributed to host defense of *Mycobacterium tuberculosis* (*Mtb*) and Zika virus [59, 60]. Interestingly, a recent study uncovered a mechanism how STING induces autophagy [61]. They elucidated that STING contains classic LC3 interacting regions (LIRs), which directly binds to LC3 and leads to the activation of autophagy [61].

Conclusion

As a crucial component in innate immune response, STING-dependent signaling has been well characterized for implication in the production of type I IFN. However, as shown in Table 1, increasing findings suggest that STING-dependent signaling also participates in the process of cell death, such as apoptosis, pyroptosis, necroptosis, and autophagy. The pro-death outcome is even predominant in certain types of cells, like lymphocytes, myeloid cells, and hepatocytes. Given that STING agonists are being tested for enhancing antitumor immune responses, more studies are warranted to elucidate the precise molecular connection between STING signaling and cell death.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ishikawa H, Barber GN. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. Nature. 2008;455(7213):674–U74. https://doi.org/10.1038/nature07317.
2. Ng KW, Marshall EA, Bell JC, Lam WL. cGAS–STING and cancer: dichotomous roles in tumor immunity and development. Trends Immunol. 2017.
3. Barber GN. STING: infection, inflammation and cancer. Nat Rev Immunol. 2015;15(12):760–70.
4. Ahn J, Barber GN. Self-DNA, STING-dependent signaling and the origins of autoinflammatory disease. Curr Opin Immunol. 2014;31:121–6. https://doi.org/10.1016/j.coi.2014.10.009.
5. 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–+. https://doi.org/10.1038/nature14156.
6. 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. https://doi.org/10.1126/science.1232458.
7. Cai X, Chiu Y-H, Chen ZJ. The cGAS-cGAMP-STING pathway of cytosolic DNA sensing and signaling. Mol Cell. 2014;54(2):289–96. https://doi.org/10.1016/j.molcel.2014.03.040.
8. Burdette DL, Monroe KM, Sotelo-Troha K, Iwig JS, Eckert B, Hyodo M, et al. STING is a direct innate immune sensor of cyclic di-GMP. Nature. 2011;478(7370):515–U111. https://doi.org/10.1038/nature10429.
9. Woodward JJ, Iavarone AT, Portnoy DA. C-di-AMP secreted by intracellular listeria monocytogenes activates a host type I interferon response. Science. 2010;328(5986):1703–5. https://doi.org/10.1126/science.1189801.
10. Corrales L, Glickman LH, McWhirter SM, Kanne DB, Sivick KE, Katibah GE, et al. Direct activation of STING in the tumor

microenvironment leads to potent and systemic tumor regression and immunity. Cell Rep. 2015;11(7):1018–30. https://doi.org/10.1016/j.celrep.2015.04.031.
11. Woo S-R, Fuertes MB, Corrales L, Spranger S, Furdyna MJ, Leung MYK, et al. STING-dependent cytosolic DNA sensing mediates innate immune recognition of immunogenic tumors. Immunity. 2014;41(5):830–42. https://doi.org/10.1016/j.immuni.2014.10.017.
12. Gao P, Zillinger T, Wang W, Ascano M, Dai P, Hartmann G, et al. Binding-pocket and lid-region substitutions render human STING sensitive to the species-specific drug DMXAA. Cell Rep. 2014;8(6):1668–76. https://doi.org/10.1016/j.celrep.2014.08.010.
13. Luo M, Wang H, Wang Z, Cai H, Lu Z, Li Y, et al. A STING-activating nanovaccine for cancer immunotherapy. Nat Nanotechnol. 2017;12(7):648–+. https://doi.org/10.1038/nnano.2017.52.
14. Fu J, Kanne DB, Leong M, Glickman LH, McWhirter SM, Lemmens E, et al. STING agonist formulated cancer vaccines can cure established tumors resistant to PD-1 blockade. Sci Transl Med. 2015;7(283):283ra52. https://doi.org/10.1126/scitranslmed.aaa4306.
15. Deng L, Liang H, Xu M, Yang X, Burnette B, Arina A, et al. STING-dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors. Immunity. 2014;41(5):843–52. https://doi.org/10.1016/j.immuni.2014.10.019.
16. Corrales L, McWhirter SM, Dubensky TW Jr, Gajewski TF. The host STING pathway at the interface of cancer and immunity. J Clin Investig. 2016;126(7):2404–11. https://doi.org/10.1172/jci86892.
17. Cheng N, Watkins-Schulz R, Junkins RD, David CN, Johnson BM, Montgomery SA, et al. A nanoparticle-incorporated STING activator enhances antitumor immunity in PD-L1-insensitive models of triple-negative breast cancer. JCI Insight. 2018;3(22). https://doi.org/10.1172/jci.insight.120638.
18. Wilson DR, Sen R, Sunshine JC, Pardoll DM, Green JJ, Kim YJ. Biodegradable STING agonist nanoparticles for enhanced cancer immunotherapy. Nanomedicine. 2018;14(2):237–46. https://doi.org/10.1016/j.nano.2017.10.013.
19. Hanson MC, Crespo MP, Abraham W, Moynihan KD, Szeto GL, Chen SH, et al. Nanoparticulate STING agonists are potent lymph node-targeted vaccine adjuvants. J Clin Invest. 2015;125(6):2532–46. https://doi.org/10.1172/JCI79915.
20. Aroh C, Wang Z, Dobbs N, Luo M, Chen Z, Gao J, et al. Innate immune activation by cGMP-AMP nanoparticles leads to potent and long-acting antiretroviral response against HIV-1. J Immunol. 2017;199(11):3840–8. https://doi.org/10.4049/jimmunol.1700972.
21. An M, Yu C, Xi J, Reyes J, Mao G, Wei WZ, et al. Induction of necrotic cell death and activation of STING in the tumor microenvironment via cationic silica nanoparticles leading to enhanced antitumor immunity. Nanoscale. 2018;10(19):9311–9. https://doi.org/10.1039/c8nr01376d.
22. 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. https://doi.org/10.1038/s41586-018-0705-y.
23. 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. https://doi.org/10.1016/j.cell.2013.09.049.
24. Gulen MF, Koch U, Haag SM, Schuler F, Apetoh L, Villunger A, et al. Signalling strength determines proapoptotic functions of STING. Nat Commun. 2017;8(1):427. https://doi.org/10.1038/s41467-017-00573-w.
25. Moretti J, Roy S, Bozec D, Martinez J, Chapman JR, Ueberheide B, et al. STING senses microbial viability to orchestrate stress-mediated autophagy of the endoplasmic reticulum. Cell. 2017;171(4):809–23 e13. https://doi.org/10.1016/j.cell.2017.09.034.
26. Tang CH, Zundell JA, Ranatunga S, Lin C, Nefedova Y, Del Valle JR, et al. Agonist-mediated activation of STING induces apoptosis in malignant B cells. Cancer Res. 2016;76(8):2137–52. https://doi.org/10.1158/0008-5472.CAN-15-1885.
27. Sze A, Belgnaoui SM, Olagnier D, Lin R, Hiscott J, van Grevenynghe J. Host restriction factor SAMHD1 limits human T cell leukemia virus type 1 infection of monocytes via STING-mediated apoptosis. Cell Host Microbe. 2013;14(4):422–34. https://doi.org/10.1016/j.chom.2013.09.009.
28. 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. https://doi.org/10.3389/fcimb.2016.00182.
29. 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. https://doi.org/10.1073/pnas.1308331110.
30. 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. https://doi.org/10.1074/jbc.M116.736991.
31. Qiao JT, Cui C, Qing L, Wang LS, He TY, Yan F, et al. Activation of the STING-IRF3 pathway promotes hepatocyte inflammation, apoptosis and induces metabolic disorders in nonalcoholic fatty liver disease. Metabolism. 2018;81:13–24. https://doi.org/10.1016/j.metabol.2017.09.010.
32. 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. https://doi.org/10.1371/journal.ppat.1006383.
33. 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. https://doi.org/10.1038/ni.3118.
34. 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. https://doi.org/10.1016/j.cell.2017.09.039.
35. Schock SN, Chandra NV, Sun Y, Irie T, Kitagawa Y, Gotoh B, et al. Induction of necroptotic cell death by viral activation of the RIG-I or STING pathway. Cell Death Differ. 2017;24(4):615–25. https://doi.org/10.1038/cdd.2016.153.
36. 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. 2018;200(8):2748–56. https://doi.org/10.4049/jimmunol.1701492.
37. Bhatelia K, Singh K, Prajapati P, Sripada L, Roy M, Singh R. MITA modulated autophagy flux promotes cell death in breast cancer cells. Cell Signal. 2017;35:73–83. https://doi.org/10.1016/j.cellsig.2017.03.024.
38. White MJ, McArthur K, Metcalf D, Lane RM, Cambier JC, Herold MJ, et al. Apoptotic caspases suppress mtDNA-induced STING-mediated type I IFN production. Cell. 2014;159(7):1549–62. https://doi.org/10.1016/j.cell.2014.11.036.
39. Rongvaux A, Jackson R, Harman CCD, Li T, West AP, de Zoete MR, et al. Apoptotic caspases prevent the induction of type I interferons by mitochondrial DNA. Cell. 2014;159(7):1563–77. https://doi.org/10.1016/j.cell.2014.11.037.

40. Larkin B, Ilyukha V, Sorokin M, Buzdin A, Vannier E, Poltorak A. Cutting edge: activation of STING in T cells induces type I IFN responses and cell death. J Immunol. 2017;199(2):397–402. https://doi.org/10.4049/jimmunol.1601999.
41. Divangahi M, Behar SM, Remold H. Dying to live: how the death modality of the infected macrophage modulates immunity to tuberculosis. In: Divangahi M, editor. New Paradigm of Immunity to Tuberculosis. Adv Exp Med Biol, 2013. p. 103–120.
42. Orzalli MH, Kagan JC. Apoptosis and necroptosis as host defense strategies to prevent viral infection. Trends Cell Biol. 2017;27(11):800–9. https://doi.org/10.1016/j.tcb.2017.05.007.
43. Chattopadhyay S, Kuzmanovic T, Zhang Y, Wetzel JL, Sen GC. Ubiquitination of the transcription factor IRF-3 activates RIPA, the apoptotic pathway that protects mice from viral pathogenesis. Immunity. 2016;44(5):1151–61. https://doi.org/10.1016/j.immuni.2016.04.009.
44. McArthur K, Whitehead LW, Heddleston JM, Li L, Padman BS, Oorschot V, et al. BAK/BAX macropores facilitate mitochondrial herniation and mtDNA efflux during apoptosis. Science. 2018;359(6378):eaao6047. https://doi.org/10.1126/science.aao6047.
45. Jorgensen I, Miao EA. Pyroptotic cell death defends against intracellular pathogens. Immunol Rev. 2015;265(1):130–42. https://doi.org/10.1111/imr.12287.
46. 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. 2016;196(7):3191–8. https://doi.org/10.4049/jimmunol.1502538.
47. 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. https://doi.org/10.1016/j.immuni.2018.07.006.
48. 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. https://doi.org/10.1073/pnas.1717190115.
49. Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. Cell. 2011;147(4):728–41. https://doi.org/10.1016/j.cell.2011.10.026.
50. Kobayashi S. Choose delicately and reuse adequately: the newly revealed process of autophagy. Biol Pharm Bull. 2015;38(8):1098–103. https://doi.org/10.1248/bpb.b15-00096.
51. Zhang Y, Whaley-Connell AT, Sowers JR, Ren J. Autophagy as an emerging target in cardiorenal metabolic disease: from pathophysiology to management. Pharmacol Ther. 2018;191:1–22. https://doi.org/10.1016/j.pharmthera.2018.06.004.
52. White E. The role for autophagy in cancer. J Clin Investig. 2015;125(1):42–6. https://doi.org/10.1172/jci73941.
53. Efeyan A, Comb WC, Sabatini DM. Nutrient-sensing mechanisms and pathways. Nature. 2015;517(7534):302–10. https://doi.org/10.1038/nature14190.
54. Kaur J, Debnath J. Autophagy at the crossroads of catabolism and anabolism. Nat Rev Mol Cell Biol. 2015;16(8):461–72. https://doi.org/10.1038/nrm4024.
55. Liu Y, Levine B. Autosis and autophagic cell death: the dark side of autophagy. Cell Death Differ. 2015;22(3):367–76. https://doi.org/10.1038/cdd.2014.143.
56. Roos WP, Thomas AD, Kaina B. DNA damage and the balance between survival and death in cancer biology. Nat Rev Cancer. 2016;16(1):20–33. https://doi.org/10.1038/nrc.2015.2.
57. Liang Q, Seo GJ, Choi YJ, Ge J, Rodgers MA, Shi M, et al. Autophagy side of MB21D1/cGAS DNA sensor. Autophagy. 2014;10(6):1146–7. https://doi.org/10.4161/auto.28769.
58. Moretti J, Blander JM. Detection of a vita-PAMP STINGs cells into reticulophagy. Autophagy. 2018;14(6):1102–4. https://doi.org/10.1080/15548627.2018.1441471.
59. Watson RO, Bell SL, MacDuff DA, Kimmey JM, Diner EJ, Olivas J, et al. The cytosolic sensor cGAS detects mycobacterium tuberculosis DNA to induce type I interferons and activate autophagy. Cell Host Microbe. 2015;17(6):811–9. https://doi.org/10.1016/j.chom.2015.05.004.
60. Liu Y, Gordesky-Gold B, Leney-Greene M, Weinbren NL, Tudor M, Cherry S. Inflammation-induced, STING-dependent autophagy restricts Zika virus infection in the drosophila brain. Cell Host Microbe. 2018;24(1):57–68 e3. https://doi.org/10.1016/j.chom.2018.05.022.
61. Liu D, Wu H, Wang C, Li Y, Tian H, Siraj S, et al. STING directly activates autophagy to tune the innate immune response. Cell Death Differ. 2018. https://doi.org/10.1038/s41418-018-0251-z.