Stimulator of Interferon Genes (STING)

Subjects: Cell Biology

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The stimulator of interferon genes (STING) is an adaptor protein involved in the activation of IFN-β and many other genes associated with the immune response activation in vertebrates. STING induction has gained attention from different angles such as the potential to trigger an early immune response against different signs of infection and cell damage, or to be used as an adjuvant in cancer immune treatments. Pharmacological control of aberrant STING activation can be used to mitigate the pathology of some autoimmune diseases. The STING structure has a well-defined ligand binding site that can harbor natural ligands such as specific purine cyclic di-nucleotides (CDN). In addition to a canonical stimulation by CDNs, other non-canonical stimuli have also been described, but the exact mechanism of some of them has not been well defined.

STING   IFN   antiviral response

1. Introduction

The stimulator of interferon genes (STING), also referred to as TMEM173, MPYS, ERIS, and MITA, is a homodimeric protein bound to the outer membrane of the endoplasmic reticulum (ER) of vertebrates. Different stimuli including DNA released by pathogens during infection, leak of nuclear or mitochondrial DNA, or the presence of cyclic di-nucleotides (CDNs) in the cytoplasm lead to the activation of STING, which results in the induction of a signaling cascade and the subsequent transcription of IFNB1 and a multitude of antiviral and proinflammatory genes [1][2].

The evolutionary origin of STING and its implications in antiviral mechanisms in different organisms have been reviewed recently by Cai and Ilmer [3]. Homologs of STING are present in many species [3]. The activation mechanisms of STING based on CDN recognition is well-conserved, even amongst some bacteria [4][5].

In mammals, STING is expressed in endothelial [6], epithelial [7], neuronal [8], and leukocytic cells, such as T cells [9], B cells [10], natural killer (NK) cells [11], macrophages, and dendritic cells (DC) [1]. STING has been described as one of the most important proteins involved in developing an antiviral response after recognizing pathogen-associated molecular patterns (PAMPs). It is involved in sensing the presence of foreign pathogens by reacting to CDNs produced endogenously by cyclic di-GMP-AMP (cGAMP) synthetase (cGAS) after binding to cytoplasmic double-stranded DNA (dsDNA) or CDNs produced by bacteria [12].

Cytosolic DNA receptors (CDRs) are pattern recognition receptors (PRRs) involved in the detection of DNA released by nuclear or mitochondrial damage or after pathogenic cell invasion. Many CDRs have been described previously. The cytosolic sensors that mediate the STING activation include cGAS; the four components of the absent in melanoma 2 (AIM2)-like receptors (ALRs), AIM2, interferon-inducible protein 16 (IFI16), interferon-inducible protein X (IFIX), DNA-dependent activator of IRFs (DAI), myeloid nuclear differentiation antigen (MNDA), helicases DHX9, DDX36, DDX41, and DExD/H box, nuclear enzymes DNA-PK, Ku70, and Ku80, RNA polymerase III, and meiotic recombination 11 homolog A (MRE11A) as reviewed by Paludan et al. [13]. Some other proteins have also been proposed as candidates for DNA sensing such as LRR binding FLII interacting protein 1 (LRRFIP1) [14].

The biological relevance of the correct activation of STING is highlighted by some STING-related interferonopathies [15]. In addition, several studies show that STING-deficient mice are more susceptible to viral infections by adenovirus and herpes simplex virus [16], as well as bacterial infections, because they cannot produce IFN-β and other cytokines in response to pathogen-derived DNA [17]. Infections by protozoan parasites can also be sensed through STING [18].

An increasing body of evidence suggests that STING also plays a role in the defense against RNA virus infections by directly detecting different viral-stimulated processes, or modulating the detection of viral RNA leading to the activation of the adaptor protein MAVS [19]. Evidence of the STING relevance against RNA viruses is highlighted by the presence of viral antagonists of the cGAS-STING pathway in different RNA viruses, such as the hepatitis C virus (HCV), yellow fever virus (YFV), or SARS-CoV-2 [16][20][21]. All this evidence shows that STING acts as a wide platform for the detection of pathogens and a promising target for triggering the antiviral response.

In addition, there are other fields where the development of STING-activating drugs has a great interest [22]. It has been demonstrated that the administration of STING agonist drugs in mice is a potent activator of the antitumoral response. Coadministration of STING ligands with other antitumor drugs such as anti-PD1/PDL1 or anti-CTL4 immunoglobulins leads to a robust immune response against tumors. For such a reason, there is a strong interest in developing STING agonists to be used in the clinic for the treatment of cancer patients [23][24].

2. cGAS-STING Canonical Signaling Pathway

Among all cellular DNA sensors, cGAS is the best characterized and considered essential for developing an innate immune response against cytosolic dsDNA [25][26]. This protein can detect pathogenic DNA or DNA released from the mitochondria or the nucleus after cell damage, even when it has been oxidized [25][27]. dsDNA fragments of more than 20 base pairs (bp) can be recognized by cGAS in a sequence-independent manner inducing its dimerization in a 2:2 DNA/cGAS complex [25][28]. Fragments of DNA smaller than 20 bp are recognized by cGAS but are unable to induce dimerization and thus do not induce its activation, while long chains of dsDNA induce the formation of ladder-like structures that result in a stronger activation of this sensor [25][29].

After the formation of dimers or higher structures, cGAS changes conformation enabling its catalytic site activation (**Figure 1**) [25][28]. Once activated, cGAS can use adenine triphosphate (ATP) and guanine triphosphate (GTP) as substrates to produce the secondary metabolite cyclic cGAMP [25][26][28]. cGAMP produced by cGAS is a CDN that contains two phosphodiester bonds, one between the 2′-OH of GMP and the 5′-phosphate of AMP and the other between the 3′-OH of AMP and the 5′-phosphate of GMP (2′3′-cGAMP). This ring-structured molecule acts as a second messenger, binding and inducing STING activation. It has also been described that cGAMP can pass to neighboring cells through gap junctions in a process dependent on connexin 43 allowing contacting cells to trigger STING activation [30].
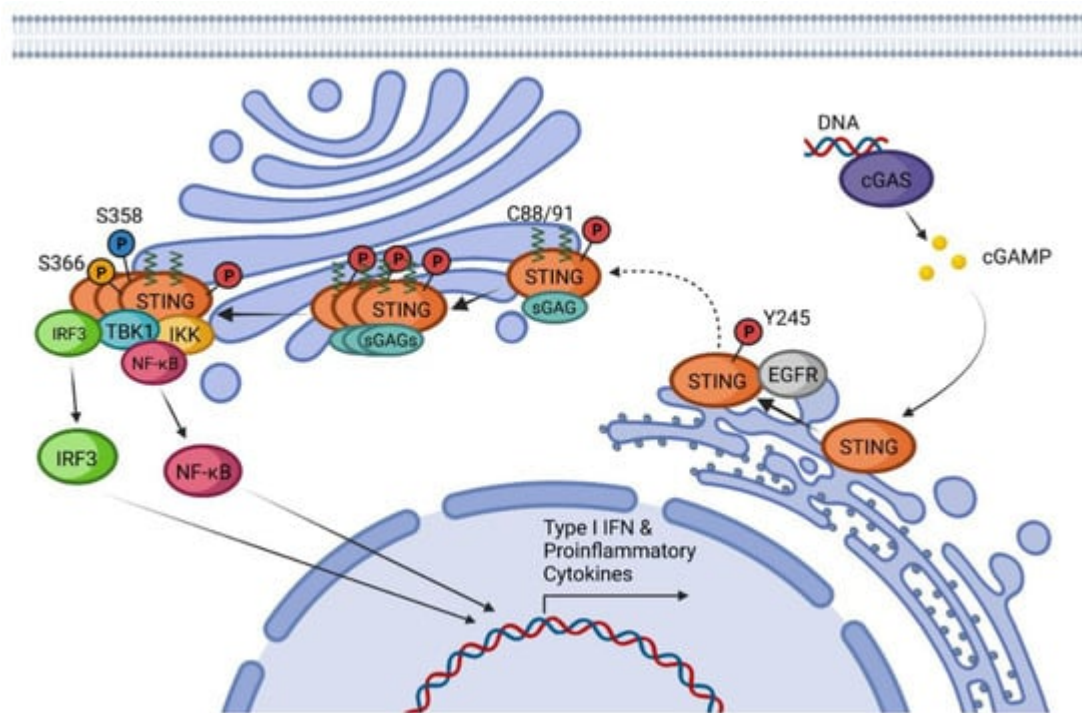

Figure 1. cGAS-STING canonical pathway: Schematic representation of STING canonical activation including post-translational modifications, modulator proteins, and main effectors involved in the production of Type I IFN and proinflammatory cytokines.

When first described, STING was proposed to directly recognize bacteria-derived CDNs such as cdiGMP, cdiAMP, and 3′3′-cGAMP, which can act as PAMPs to activate the immune responses during infection [31].

In addition to interacting with STING in host cells, CDNs play a pivotal role as second messengers controlling physiological processes in bacteria [32][33]. Moreover, these molecules appear to modulate many behaviors facets at the bacteria community level, such as *quorum sensing*, the formation of aggregates, swarming motility, or the formation of bacterial biofilms [34][35]. There is a correlation between high intracellular levels of cdiGMP and biofilm formation and a sessile lifestyle. In contrast, low cdiGMP levels are associated with a motile or planktonic existence [36]. 3′3′-cGAMP also has been related to protection against phage infections in bacteria [37].

Inactive resting STING forms a homodimer that suffers a 180° twist and several conformational changes upon CDN-binding [38][39]. Conformational changes of STING after CDN activation promote the binding to the epidermal growth factor receptor (EGFR) in the ER, causing EGFR auto-phosphorylation at Y1068 and its consequent activation. Activated EGFR also phosphorylates STING at Y245 [40]. STING translocates from the ER to the Golgi apparatus by passing through the ER-Golgi intermediate compartment (ERGIC) [41]. The translocation process is driven by the STING-iRhom2-TRAPβ complex [42]. It is also known that K63-linked ubiquitination is required for STING trafficking, but it is not completely clear if this modification is produced on resting STING or after activation by CDNs [43].

Once in the Golgi, STING binds to sulfated glycosaminoglycans (sGAGs) and is palmitoylated in C88 and C91, with these two modifications being necessary to induce STING polymerization and the formation of oligomers [44][45]. Mukai et al. demonstrated by tritylation experiments that of the 23 human-encoded palmitoyl transferases (DHHCs), those responsible for the palmitoylation of STING are DHHC3, DHHC7, and DHHC15 [45]. This oligomerization is required for the signal transduction and activation of STING effectors [44][45]. It has been proposed that C88 and C91 palmitoylation induces the STING clustering into lipid rafts from the cytosolic side of the Golgi while sGAGs promote STING polymerization from the lumen [45]. After oligomerization, STING recruits and activates the downstream effector kinase TBK1 [28]. Activated TBK1 dimerizes and induces its autophosphorylation and phosphorylation of STING in two different residues, S358 and S366 [28][46][47][48]. As the first step, TBK1 phosphorylates S358, stabilizing the STING-TBK1 complex. The kinase domain of TBK1 cannot phosphorylate S366 since it is bound to this region of STING. To achieve S366 phosphorylation, TBK1 requires the previous formation of STING oligomers so that the kinase domain reaches S366 of the neighboring STING-TBK1 complexes [46].

The TBK1-STING phosphorylated complex recruits and phosphorylates Interferon Regulatory Factor 3 (IRF3) inducing its dimerization and translocation into the nucleus, which results in the expression of type I IFNs, a set of Interferon-Stimulated Genes (ISGs) and proinflammatory cytokines [49]. IRF3 is not the only transcription factor that STING can recruit. STING activation has been shown to induce the activation of IKKε, which in a redundant combination with TBK1 can induce the phosphorylation and translocation of NF-κB [50]. STING-dependent activation of NF-κB is responsible for the production of proinflammatory cytokines such as IL-6, IL-12, or TNF-α [28][51]. All these effects together lead to the development of an antiviral state and trigger innate and adaptive immune responses.

STING activation has been linked to other biological effects in addition to IFN and proinflammatory cytokines production. It is well known that STING activation triggers autophagy in a process that is independent of TBK1, IFN, and the Unc-51-Like Autophagy Activating Kinase (ULK) [28][52][53]. STING induction of autophagy is necessary for cytosolic DNA and virus clearance and the depletion of activated STING structures [30][52]. Once STING is activated, it initiates a translocation from ER to the Golgi apparatus as described before. During this process, STING passes through the ERGIC intermediate compartment in a coat complex protein II (COPII) and ADP-ribosylation factor (ARF) GTPase-dependent manner [52]. STING containing ERGIC induces light chain 3 (LC3) lipidation into LC3-II, a classic effector of autophagy, in a process dependent on ATG5 and WIPI2 [30][52][54].

Although autophagy has not been related to the induction of type I IFN expression, its implication in the IFN system seems to provide a downregulation of PRRs and receptors whose abundance is necessary to avoid tissue damage produced by excessive immune stimulation [55].

3. STING Non-Canonical Signaling Pathway

The activation of STING is possible even in the absence of cGAS, 2′3′-cGAMP, or other CDNs as inducers (**Figure 2**) [56][57]. Until now, different cGAS-independent mechanisms of STING activation have been described.
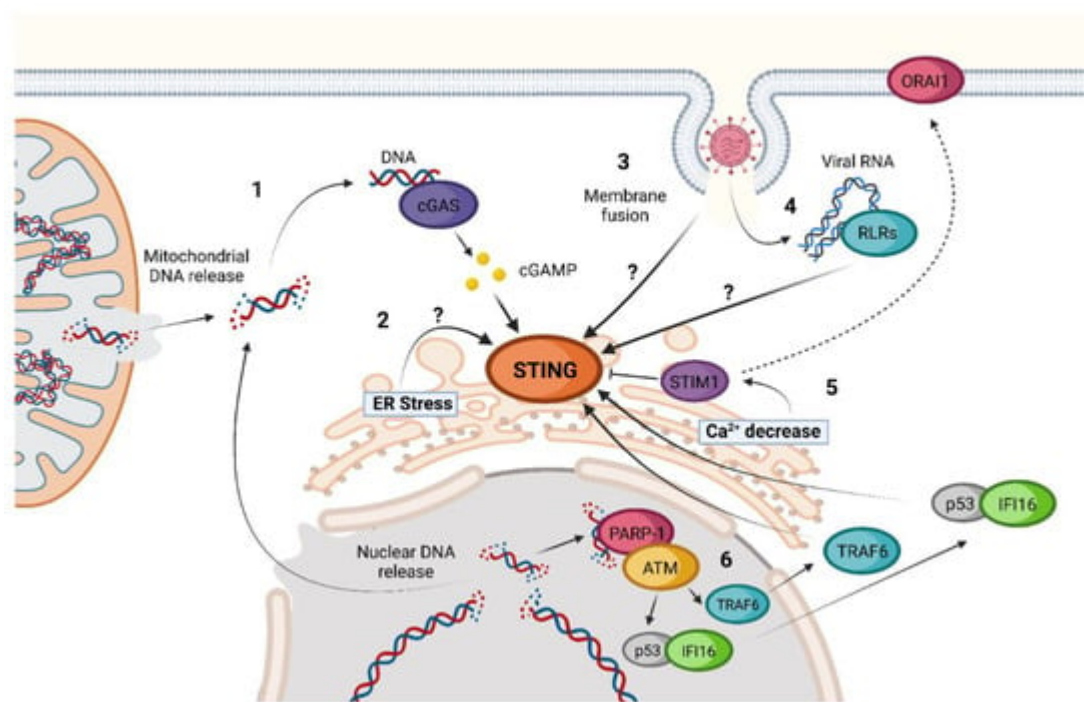

Figure 2. Non-canonical activations of STING. **1.** Release of nuclear or mitochondrial DNA into the cytoplasm during viral infection or after cell damage. **2.** Activation of the STING–TBK1–IRF3 axis by ER-stress inducers such as ethanol. **3.** cGAS-independent activation of STING triggered by membrane fusion. **4.** Activation of STING by RIG-I-like Receptors (RLRs) after detection of viral RNA in a MAVS-independent process. **5.** Ca^{2+} depletion in the ER triggers activation of STIM1 sensor, an inhibitor of STING, and induces its migration to join the calcium channel ORAI1, increasing STING activity. **6.** IFI16 pathway of nuclear-damaged DNA detection in the absence of cGAS activation. Question marks (?) represent "unknown activation mechanism".

Interferon Gamma Inducible Protein 16 (IFI16) is a DNA sensor located in the cytosol and the nucleus and has been proven to be both a coactivator in the classic cGAS-STING pathway and a cGAS-independent STING inducer [58]. In the canonical pathway, IFI16 is necessary for the 2′3′-cGAMP production by stabilizing the cGAS–DNA interaction and for the STING activation of TBK1, at least in some cell types [58][59].

The proposed IFI16-dependent non-canonical activation of STING begins with polyADP-ribose polymerase-1 (PARP-1) and ataxia telangiectasia mutated (ATM) detection of damaged DNA in the nucleus. After this

recognition, ATM phosphorylates p53, inducing the recruitment of IFI16. The complex p53-IFI16 translocases to the cytoplasm and is capable of interacting with TRAF6. Once activated, TRAF6 induces the formation of multiple K63-linked ubiquitin chains on STING. This ubiquitination leads to a non-canonical process of STING activation [58]. IFI16-dependent activation of STING takes place without STING phosphorylation in S366, TBK1 recruitment, or trafficking to ERGIC, leading to a predominant activation of NF-κB instead of IRF3 as compared to the canonical cGAS-STING pathway [58].

Another non-canonical activation of STING that has been proposed is through ER stress induction [57]. It has been suggested that ethanol can induce STING-TBK1-IRF3 activation in a not-very-well-characterized ER stress-dependent activation. This activation leads to IRF3-dependent Type I IFN induction and apoptosis through B-cell lymphoma 2 (Bcl2)-associated X protein (BAX) activation [57]. Many viruses, such as herpes simplex virus (HSV) or West Nile virus (WNV), amongst others [60], can induce ER stress during infection [61][62]. Thus, understanding how this ER stress-dependent activation of STING works can be important to understand better host defense against infections.

Calcium cell homeostasis seems to influence STING activation as well [57]. Stromal Interaction Molecule 1 (STIM1) is a Ca^{2+} sensor that is in the ER and interacts with inactivated STING. Due to this interaction, inactivated STIM1 acts as a natural inhibitor of STING oligomerization and trafficking [56][57]. STIM1 knock-out cells have basal levels of STING activation and IFN expression that are higher than those present in cells that present a normal STIM1 expression [56][57]. Under ER Ca^{2+} depletion conditions, STIM1 suffers a conformational change that enables the interaction with calcium release-activated calcium channel protein 1 (ORAI1) [63]. This way, STIM1 has been proposed separately to facilitate STING activation. As for the case of ER stress, many viruses have shown ER Ca^{2+} alterations during infection, making it another possibility for triggering innate immunity through these changes [64].

Different studies have linked STING activation to RNA virus infections [62][65][66][67]. A hint of the relevance of STING in the innate immune response to RNA virus infection is that many RNA viruses have developed mechanisms to inhibit STING pathway activation [68][69][70][71].

Mechanisms of STING activation by these viruses seem diverse, and some remain unclear. One of the most evident is the indirect activation of the classical cGAS-STING pathway by the detection of mitochondrial DNA (mDNA) released due to the increase in ROS and the activation of the inflammasome during dengue virus (DENV) infection [72][73]. Another example is the detection of damaged nuclear DNA as a result of SARS-CoV-2 spike protein expression associated with infection. Due to its main role as a fusion protein, the expression of the Spike under SARS-CoV-2 infection leads to the formation of multinucleated syncytial cells in which damaged nuclei produce micronuclei, which, in turn, are detected by cGAS [74][75]. Meanwhile, membrane fusion has been proven to induce cGAS-independent STING activation that leads to TBK1 and IRF3 activation and the type I IFN response [76][77]. Influenza A virus (IAV) blocks this signaling through a direct interaction between Hemagglutinin (HA) fusion peptide (FP) and STING, preventing TBK1 activation and STING phosphorylation [77]. The exact mechanism by which membrane fusion activates STING has not been addressed. Another role of STING under RNA viral

infections seems to be blocking the translation of viral and host proteins [67]. This activation of STING is dependent on classic cytosolic RNA sensors and RLR but is MAVS-independent and does not result in IFN expression or autophagy induction [67]. Different studies have shown this link between STING and RLR, but the mechanism is still unknown [1][78].

References

1. Ishikawa, H.; Barber, G.N. STING is an Endoplasmic Reticulum Adaptor that Facilitates Innate Immune Signalling. Nature 2008, 455, 674–678.

2. Barber, G.N. STING: Infection, Inflammation, and Cancer. Nat. Rev. Immunol. 2015, 15, 760–770.

3. Cai, H.; Imler, J. cGAS-STING: Insight on the Evolution of a Primordial Antiviral Signaling Cassette. Fac. Rev. 2021, 10, 54.

4. Kranzusch, P.J. cGAS and CD-NTase Enzymes: Structure, Mechanism, and Evolution. Curr. Opin. Struct. Biol. 2019, 59, 178–187.

5. Morehouse, B.R.; Govande, A.A.; Millman, A.; Keszei, A.F.A.; Lowey, B.; Ofir, G.; Shao, S.; Sorek, R.; Kranzusch, P.J. STING Cyclic Dinucleotide Sensing Originated in Bacteria. Nature 2020, 586, 429–433.

6. Anastasiou, M.; Newton, G.A.; Kaur, K.; Carrillo-Salinas, F.J.; Smolgovsky, S.A.; Bayer, A.L.; Ilyukha, V.; Sharma, S.; Poltorak, A.; Luscinskas, F.W.; et al. Endothelial STING Controls T Cell Transmigration in an IFNI-Dependent Manner. JCI Insight. 2021, 6, e149346.

7. Yu, Y.; Yang, W.; Bilotta, A.J.; Yu, Y.; Zhao, X.; Zhou, Z.; Yao, S.; Xu, J.; Zhou, J.; Dann, S.M.; et al. STING Controls Intestinal Homeostasis through Promoting Antimicrobial Peptide Expression in Epithelial Cells. FASEB J. 2020, 34, 15417–15430.

8. Nazmi, A.; Mukhopadhyay, R.; Dutta, K.; Basu, A. STING Mediates Neuronal Innate Immune Response Following Japanese Encephalitis Virus Infection. Sci. Rep. 2012, 2, 347.

9. 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, 397–402.

10. Walker, M.M.; Crute, B.W.; Cambier, J.C.; Getahun, A. B Cell-Intrinsic STING Signaling Triggers Cell Activation, Synergizes with B Cell Receptor Signals, and Promotes Antibody Responses. J. Immunol. 2018, 201, 2641–2653.

11. Souza-Fonseca-Guimaraes, F.; Parlato, M.; de Oliveira, R.B.; Golenbock, D.; Fitzgerald, K.; Shalova, I.N.; Biswas, S.K.; Cavaillon, J.; Adib-Conquy, M. Interferon-Γ and Granulocyte/Monocyte Colony-Stimulating Factor Production by Natural Killer Cells Involves

Different Signaling Pathways and the Adaptor Stimulator of Interferon Genes (STING). J. Biol. Chem. 2013, 288, 10715–10721.

12. Margolis, S.R.; Wilson, S.C.; Vance, R.E. Evolutionary Origins of cGAS-STING Signaling. Trends Immunol. 2017, 38, 733–743.

13. Paludan, S.R.; Bowie, A.G. Immune Sensing of DNA. Immunity 2013, 38, 870–880.

14. Yang, P.; An, H.; Liu, X.; Wen, M.; Zheng, Y.; Rui, Y.; Cao, X. The Cytosolic Nucleic Acid Sensor LRRFIP1 Mediates the Production of Type I Interferon Via a Beta-Catenin-Dependent Pathway. Nat. Immunol. 2010, 11, 487–494.

15. Lin, B.; Goldbach-Mansky, R. Pathogenic Insights from Genetic Causes of Autoinflammatory Inflammasomopathies and Interferonopathies. J. Allergy Clin. Immunol. 2022, 149, 819–832.

16. Ishikawa, H.; Ma, Z.; Barber, G.N. STING Regulates Intracellular DNA-Mediated, Type I Interferon-Dependent Innate Immunity. Nature 2009, 461, 788–792.

17. Li, X.; Wu, J.; Gao, D.; Wang, H.; Sun, L.; Chen, Z.J. Pivotal Roles of cGAS-cGAMP Signaling in Antiviral Defense and Immune Adjuvant Effects. Science 2013, 341, 1390–1394.

18. Sun, Y.; Cheng, Y. STING Or Sting: cGAS-STING-Mediated Immune Response to Protozoan Parasites. Trends Parasitol. 2020, 36, 773–784.

19. Webb, L.G.; Fernandez-Sesma, A. RNA Viruses, and the cGAS-STING Pathway: Reframing our Understanding of Innate Immune Sensing. Curr. Opin. Virol. 2022, 53, 101206.

20. Nitta, S.; Sakamoto, N.; Nakagawa, M.; Kakinuma, S.; Mishima, K.; Kusano-Kitazume, A.; Kiyohashi, K.; Murakawa, M.; Nishimura-Sakurai, Y.; Azuma, S.; et al. Hepatitis C Virus NS4B Protein Targets STING and Abrogates RIG-I-Mediated Type I Interferon-Dependent Innate Immunity. Hepatology 2013, 57, 46–58.

21. Rui, Y.; Su, J.; Shen, S.; Hu, Y.; Huang, D.; Zheng, W.; Lou, M.; Shi, Y.; Wang, M.; Chen, S.; et al. Unique and Complementary Suppression of cGAS-STING and RNA Sensing-Triggered Innate Immune Responses by SARS-CoV-2 Proteins. Signal Transduct. Target. Ther. 2021, 6, 123.

22. Corrales, L.; McWhirter, S.M.; Dubensky, T.W.; Gajewski, T.F. The Host STING Pathway at the Interface of Cancer and Immunity. J. Clin. Investig. 2016, 126, 2404–2411.

23. Foote, J.B.; Kok, M.; Leatherman, J.M.; Armstrong, T.D.; Marcinkowski, B.C.; Ojalvo, L.S.; Kanne, D.B.; Jaffee, E.M.; Dubensky, T.W.; Emens, L.A. A STING Agonist Given with OX40 Receptor and PD-L1 Modulators Primes Immunity and Reduces Tumor Growth in Tolerized Mice. Cancer Immunol. Res. 2017, 5, 468–479.

24. Demaria, O.; De Gassart, A.; Coso, S.; Gestermann, N.; Di Domizio, J.; Flatz, L.; Gaide, O.; Michielin, O.; Hwu, P.; Petrova, T.V.; et al. STING Activation of Tumor Endothelial Cells Initiates

Spontaneous and Therapeutic Antitumor Immunity. Proc. Natl. Acad. Sci. USA 2015, 112, 15408–15413.

25. Yu, L.; Liu, P. Cytosolic DNA Sensing by cGAS: Regulation, Function, and Human Diseases. Signal Transduct. Target. Ther. 2021, 6, 170.

26. Sun, L.; Wu, J.; Du, F.; Chen, X.; Chen, Z.J. Cyclic GMP-AMP Synthase is a Cytosolic DNA Sensor that Activates the Type I Interferon Pathway. Science 2013, 339, 786–791.

27. Gehrke, N.; Mertens, C.; Zillinger, T.; Wenzel, J.; Bald, T.; Zahn, S.; Tüting, T.; Hartmann, G.; Barchet, W. Oxidative Damage of DNA Confers Resistance to Cytosolic Nuclease TREX1 Degradation and Potentiates STING-Dependent Immune Sensing. Immunity 2013, 39, 482–495.

28. Decout, A.; Katz, J.D.; Venkatraman, S.; Ablasser, A. The cGAS-STING Pathway as a Therapeutic Target in Inflammatory Diseases. Nat. Rev. Immunol. 2021, 21, 548–569.

29. Luecke, S.; Holleufer, A.; Christensen, M.H.; Jønsson, K.L.; Boni, G.A.; Sørensen, L.K.; Johannsen, M.; Jakobsen, M.R.; Hartmann, R.; Paludan, S.R. cGAS is Activated by DNA in a Length-Dependent Manner. EMBO Rep. 2017, 18, 1707–1715.

30. Wan, D.; Jiang, W.; Hao, J. Research Advances in how the cGAS-STING Pathway Controls the Cellular Inflammatory Response. Front. Immunol. 2020, 11, 615.

31. Burdette, D.L.; Monroe, K.M.; Sotelo-Troha, K.; Iwig, J.S.; Eckert, B.; Hyodo, M.; Hayakawa, Y.; Vance, R.E. STING is a Direct Innate Immune Sensor of Cyclic Di-GMP. Nature 2011, 478, 515–518.

32. Gürsoy, U.K.; Gürsoy, M.; Könönen, E.; Sintim, H.O. Cyclic Dinucleotides in Oral Bacteria and in Oral Biofilms. Front. Cell. Infect. Microbiol. 2017, 7, 273.

33. Devaux, L.; Sleiman, D.; Mazzuoli, M.; Gominet, M.; Lanotte, P.; Trieu-Cuot, P.; Kaminski, P.; Firon, A. Cyclic Di-AMP Regulation of Osmotic Homeostasis is Essential in Group B Streptococcus. PLoS Genet. 2018, 14, e1007342.

34. Purcell, E.B.; Tamayo, R. Cyclic Diguanylate Signaling in Gram-Positive Bacteria. FEMS Microbiol. Rev. 2016, 40, 753–773.

35. Randall, T.E.; Eckartt, K.; Kakumanu, S.; Price-Whelan, A.; Dietrich, L.E.P.; Harrison, J.J. Sensory Perception in Bacterial Cyclic Diguanylate Signal Transduction. J. Bacteriol. 2022, 204, e0043321.

36. Ha, D.; O'Toole, G.A. C-Di-GMP and its Effects on Biofilm Formation and Dispersion: A Pseudomonas Aeruginosa Review. Microbiol. Spectr. 2015, 3, MB-2014.

37. Cohen, D.; Melamed, S.; Millman, A.; Shulman, G.; Oppenheimer-Shaanan, Y.; Kacen, A.; Doron, S.; Amitai, G.; Sorek, R. Cyclic GMP-AMP Signalling Protects Bacteria Against Viral Infection. Nature 2019, 574, 691–695.

38. Ergun, S.L.; Fernandez, D.; Weiss, T.M.; Li, L. STING Polymer Structure Reveals Mechanisms for Activation, Hyperactivation, and Inhibition. Cell 2019, 178, 290–301.e10.

39. Shang, G.; Zhang, C.; Chen, Z.J.; Bai, X.; Zhang, X. Cryo-EM Structures of STING Reveal its Mechanism of Activation by Cyclic GMP-AMP. Nature 2019, 567, 389–393.

40. Wang, C.; Wang, X.; Veleeparambil, M.; Kessler, P.M.; Willard, B.; Chattopadhyay, S.; Sen, G.C. EGFR-Mediated Tyrosine Phosphorylation of STING Determines its Trafficking Route and Cellular Innate Immunity Functions. EMBO J. 2020, 39, e104106.

41. Dobbs, N.; Burnaevskiy, N.; Chen, D.; Gonugunta, V.K.; Alto, N.M.; Yan, N. STING Activation by Translocation from the ER is Associated with Infection and Autoinflammatory Disease. Cell Host Microbe 2015, 18, 157–168.

42. Luo, W.; Li, S.; Li, C.; Lian, H.; Yang, Q.; Zhong, B.; Shu, H. iRhom2 is Essential for Innate Immunity to DNA Viruses by Mediating Trafficking and Stability of the Adaptor STING. Nat. Immunol. 2016, 17, 1057–1066.

43. Ni, G.; Konno, H.; Barber, G.N. Ubiquitination of STING at Lysine 224 Controls IRF3 Activation. Sci. Immunol. 2017, 2, eaah7119.

44. Fang, R.; Jiang, Q.; Guan, Y.; Gao, P.; Zhang, R.; Zhao, Z.; Jiang, Z. Golgi Apparatus-Synthesized Sulfated Glycosaminoglycans Mediate Polymerization and Activation of the cGAMP Sensor STING. Immunity 2021, 54, 962–975.e8.

45. Mukai, K.; Konno, H.; Akiba, T.; Uemura, T.; Waguri, S.; Kobayashi, T.; Barber, G.N.; Arai, H.; Taguchi, T. Activation of STING Requires Palmitoylation at the Golgi. Nat. Commun. 2016, 7, 11932.

46. Zhang, C.; Shang, G.; Gui, X.; Zhang, X.; Bai, X.; Chen, Z.J. Structural Basis of STING Binding with and Phosphorylation by TBK1. Nature 2019, 567, 394–398.

47. Yu, Y.; Liu, J.; Liu, C.; Liu, R.; Liu, L.; Yu, Z.; Zhuang, J.; Sun, C. Post-Translational Modifications of cGAS-STING: A Critical Switch for Immune Regulation. Cells 2022, 11, 3043.

48. Li, Z.; Liu, G.; Sun, L.; Teng, Y.; Guo, X.; Jia, J.; Sha, J.; Yang, X.; Chen, D.; Sun, Q. PPM1A Regulates Antiviral Signaling by Antagonizing TBK1-Mediated STING Phosphorylation and Aggregation. PLoS Pathog. 2015, 11, e1004783.

49. Tamura, T.; Yanai, H.; Savitsky, D.; Taniguchi, T. The IRF Family Transcription Factors in Immunity and Oncogenesis. Annu. Rev. Immunol. 2008, 26, 535–584.

50. Balka, K.R.; Louis, C.; Saunders, T.L.; Smith, A.M.; Calleja, D.J.; D'Silva, D.B.; Moghaddas, F.; Tailler, M.; Lawlor, K.E.; Zhan, Y.; et al. TBK1 and IKKε Act Redundantly to Mediate STING-Induced NF-κB Responses in Myeloid Cells. Cell Rep. 2020, 31, 107492.

51. Zhu, Q.; Man, S.M.; Gurung, P.; Liu, Z.; Vogel, P.; Lamkanfi, M.; Kanneganti, T. Cutting Edge: STING Mediates Protection Against Colorectal Tumorigenesis by Governing the Magnitude of Intestinal Inflammation. J. Immunol. 2014, 193, 4779–4782.

52. Gui, X.; Yang, H.; Li, T.; Tan, X.; Shi, P.; Li, M.; Du, F.; Chen, Z.J. Autophagy Induction Via STING Trafficking is a Primordial Function of the cGAS Pathway. Nature 2019, 567, 262–266.

53. Zhang, R.; Kang, R.; Tang, D. The STING1 Network Regulates Autophagy and Cell Death. Signal Transduct. Target. Ther. 2021, 6, 208.

54. Liu, D.; Wu, H.; Wang, C.; Li, Y.; Tian, H.; Siraj, S.; Sehgal, S.A.; Wang, X.; Wang, J.; Shang, Y.; et al. STING Directly Activates Autophagy to Tune the Innate Immune Response. Cell Death Differ. 2019, 26, 1735–1749.

55. Tian, Y.; Wang, M.; Zhao, J. Crosstalk between Autophagy and Type I Interferon Responses in Innate Antiviral Immunity. Viruses 2019, 11, 132.

56. Srikanth, S.; Woo, J.S.; Wu, B.; El-Sherbiny, Y.M.; Leung, J.; Chupradit, K.; Rice, L.; Seo, G.J.; Calmettes, G.; Ramakrishna, C.; et al. The Ca2+ Sensor STIM1 Regulates the Type I Interferon Response by Retaining the Signaling Adaptor STING at the Endoplasmic Reticulum. Nat. Immunol. 2019, 20, 152–162.

57. Petrasek, J.; Iracheta-Vellve, A.; Csak, T.; Satishchandran, A.; Kodys, K.; Kurt-Jones, E.A.; Fitzgerald, K.A.; Szabo, G. STING-IRF3 Pathway Links Endoplasmic Reticulum Stress with Hepatocyte Apoptosis in Early Alcoholic Liver Disease. Proc. Natl. Acad. Sci. USA 2013, 110, 16544–16549.

58. Dunphy, G.; Flannery, S.M.; Almine, J.F.; Connolly, D.J.; Paulus, C.; Jønsson, K.L.; Jakobsen, M.R.; Nevels, M.M.; Bowie, A.G.; Unterholzner, L. Non-Canonical Activation of the DNA Sensing Adaptor STING by ATM and IFI16 Mediates NF-κB Signaling After Nuclear DNA Damage. Mol. Cell 2018, 71, 745–760.e5.

59. Jønsson, K.L.; Laustsen, A.; Krapp, C.; Skipper, K.A.; Thavachelvam, K.; Hotter, D.; Egedal, J.H.; Kjolby, M.; Mohammadi, P.; Prabakaran, T.; et al. IFI16 is Required for DNA Sensing in Human Macrophages by Promoting Production and Function of cGAMP. Nat. Commun. 2017, 8, 14391.

60. Li, S.; Kong, L.; Yu, X. The Expanding Roles of Endoplasmic Reticulum Stress in Virus Replication and Pathogenesis. Crit. Rev. Microbiol. 2015, 41, 150–164.

61. Choi, J.; Song, C. Insights into the Role of Endoplasmic Reticulum Stress in Infectious Diseases. Front. Immunol. 2019, 10, 3147.

62. McGuckin Wuertz, K.; Treuting, P.M.; Hemann, E.A.; Esser-Nobis, K.; Snyder, A.G.; Graham, J.B.; Daniels, B.P.; Wilkins, C.; Snyder, J.M.; Voss, K.M.; et al. STING is Required for Host Defense Against Neuropathological West Nile Virus Infection. PLoS Pathog. 2019, 15, e1007899.

63. Chen, Y.; Chen, Y.; Chen, Y.; Chiu, W.; Shen, M. The STIM1-Orai1 Pathway of Store-Operated Ca2+ Entry Controls the Checkpoint in Cell Cycle G1/S Transition. Sci. Rep. 2016, 6, 22142.

64. Mekahli, D.; Bultynck, G.; Parys, J.B.; De Smedt, H.; Missiaen, L. Endoplasmic-Reticulum Calcium Depletion and Disease. Cold Spring Harb. Perspect. Biol. 2011, 3, a004317.

65. Wrighton, K. The STING Behind Dengue Virus Infection. Nat. Rev. Microbiol. 2018, 16, 330.

66. Ni, G.; Ma, Z.; Damania, B. cGAS and STING: At the Intersection of DNA and RNA Virus-Sensing Networks. PLoS Pathog. 2018, 14, e1007148.

67. Franz, K.M.; Neidermyer, W.J.; Tan, Y.; Whelan, S.P.J.; Kagan, J.C. STING-Dependent Translation Inhibition Restricts RNA Virus Replication. Proc. Natl. Acad. Sci. USA 2018, 115, E2058–E2067.

68. Webb, L.G.; Veloz, J.; Pintado-Silva, J.; Zhu, T.; Rangel, M.V.; Mutetwa, T.; Zhang, L.; Bernal-Rubio, D.; Figueroa, D.; Carrau, L.; et al. Chikungunya Virus Antagonizes cGAS-STING Mediated Type-I Interferon Responses by Degrading cGAS. PLoS Pathog. 2020, 16, e1008999.

69. Aguirre, S.; Maestre, A.M.; Pagni, S.; Patel, J.R.; Savage, T.; Gutman, D.; Maringer, K.; Bernal-Rubio, D.; Shabman, R.S.; Simon, V.; et al. DENV Inhibits Type I IFN Production in Infected Cells by Cleaving Human STING. PLoS Pathog. 2012, 8, e1002934.

70. Ding, Q.; Cao, X.; Lu, J.; Huang, B.; Liu, Y.; Kato, N.; Shu, H.; Zhong, J. Hepatitis C Virus NS4B Blocks the Interaction of STING and TBK1 to Evade Host Innate Immunity. J. Hepatol. 2013, 59, 52–58.

71. Sun, L.; Xing, Y.; Chen, X.; Zheng, Y.; Yang, Y.; Nichols, D.B.; Clementz, M.A.; Banach, B.S.; Li, K.; Baker, S.C.; et al. Coronavirus Papain-Like Proteases Negatively Regulate Antiviral Innate Immune Response through Disruption of STING-Mediated Signaling. PLoS ONE 2012, 7, e30802.

72. Aguirre, S.; Luthra, P.; Sanchez-Aparicio, M.T.; Maestre, A.M.; Patel, J.; Lamothe, F.; Fredericks, A.C.; Tripathi, S.; Zhu, T.; Pintado-Silva, J.; et al. Dengue Virus NS2B Protein Targets cGAS for Degradation and Prevents Mitochondrial DNA Sensing during Infection. Nat. Microbiol. 2017, 2, 17037.

73. Lai, J.; Wang, M.; Huang, C.; Wu, C.; Hung, L.; Yang, C.; Ke, P.; Luo, S.; Liu, S.; Ho, L. Infection with the Dengue RNA Virus Activates TLR9 Signaling in Human Dendritic Cells. EMBO Rep. 2018, 19, e46182.

74. Sun, B.; Sundström, K.B.; Chew, J.J.; Bist, P.; Gan, E.S.; Tan, H.C.; Goh, K.C.; Chawla, T.; Tang, C.K.; Ooi, E.E. Dengue Virus Activates cGAS through the Release of Mitochondrial DNA. Sci. Rep. 2017, 7, 3594.

75. Liu, X.; Wei, L.; Xu, F.; Zhao, F.; Huang, Y.; Fan, Z.; Mei, S.; Hu, Y.; Zhai, L.; Guo, J.; et al. SARS-CoV-2 Spike Protein-Induced Cell Fusion Activates the cGAS-STING Pathway and the Interferon Response. Sci. Signal. 2022, 15, eabg8744.

76. Holm, C.K.; Jensen, S.B.; Jakobsen, M.R.; Cheshenko, N.; Horan, K.A.; Moeller, H.B.; Gonzalez-Dosal, R.; Rasmussen, S.B.; Christensen, M.H.; Yarovinsky, T.O.; et al. Virus-Cell Fusion as a Trigger of Innate Immunity Dependent on the Adaptor STING. Nat. Immunol. 2012, 13, 737–743.

77. Holm, C.K.; Rahbek, S.H.; Gad, H.H.; Bak, R.O.; Jakobsen, M.R.; Jiang, Z.; Hansen, A.L.; Jensen, S.K.; Sun, C.; Thomsen, M.K.; et al. Influenza A Virus Targets a cGAS-Independent STING Pathway that Controls Enveloped RNA Viruses. Nat. Commun. 2016, 7, 10680.

78. Liu, Y.; Goulet, M.; Sze, A.; Hadj, S.B.; Belgnaoui, S.M.; Lababidi, R.R.; Zheng, C.; Fritz, J.H.; Olagnier, D.; Lin, R. RIG-I-Mediated STING Upregulation Restricts Herpes Simplex Virus 1 Infection. J. Virol. 2016, 90, 9406–9419.