# The cGAS-cGAMP-STING Pathway: A Molecular Link Between Immunity and Metabolism

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**It has been appreciated for many years that there is a strong association between metabolism and immunity in advanced metazoan organisms. Distinct immune signatures and signaling pathways have been found not only in immune but also in metabolic cells. The newly discovered DNA-sensing cGAS-cGAMP-STING pathway mediates type I interferon inflammatory responses in immune cells to defend against viral and bacterial infections. Recent studies show that this pathway is also activated by host DNA aberrantly localized in the cytosol, contributing to increased sterile inflammation, insulin resistance, and the development of nonalcoholic fatty liver disease (NAFLD). Potential interactions of the cGAS-cGAMP-STING pathway with mTORC1 signaling, autophagy, and apoptosis have been reported, suggesting an important role of the cGAS-cGAMP-STING pathway in the networking and coordination of these important biological processes. However, the regulation, mechanism of action, and tissue-specific role of the cGAS-cGAMP-STING signaling pathway in metabolic disorders remain largely elusive. It is also unclear whether targeting this signaling pathway is effective for the prevention and treatment of obesity-induced metabolic diseases. Answers to these questions would provide new insights for developing effective therapeutic interventions for metabolic diseases such as insulin resistance, NAFLD, and type 2 diabetes.**

For maintenance of normal physiological function, a living organism needs to obtain nutrients from the environment and convert it into energy through its metabolic system. Meanwhile, the organism has to protect itself from attacks of potential pathogenic invaders. Evolutionarily, it is not surprising that the functions of the immune and metabolic systems are closely linked and coordinated. It is well known that an effective immune response is highly energy dependent in order to activate innate immunity and promote adaptive immunity in response to various environmental insults. Under conditions of energy insufficiency such as famine, prolonged and intensive physical activities, and overloaded neuronal and cardiovascular functions, the immune responses in an organism may be sacrificed, leading to increased infections and other immune-related defects (1). On the other hand, overnutrition may lead to overactivated immunity, resulting in inflammation and related metabolic diseases such as insulin resistance and type 2 diabetes (2). To maintain homeostasis, an organism thus codevelops the immune and metabolic systems to adapt to environmental changes. Although metabolic cells and tissue-resident immune cells exert distinct functions, numerous studies have already demonstrated that these cells undergo intensive and dynamic cross talks to coordinate their action in preserving homeostasis. Emerging evidence accumulated over the past several years also reveals the presence of distinct immune signatures and signaling pathways in key metabolic cells and vice versa, further signifying an integral link between immune activity and metabolic function.

## Activation of the cGAS-cGAMP-STING Pathway in Immunity

Over the past several years, a key DNA immune response pathway, the cGAMP synthase (cGAS [also known as Mb21d1])–cGAMP–stimulator of interferon genes (STING [also called TMEM173, MITA, MPYS, and ERIS]) pathway, has been discovered in immune cells. The cGAS-cGAMP-STING pathway was originally identified as a signaling cascade that is activated by double-stranded DNA (dsDNA) during pathogen infections. cGAS senses viral and bacterial dsDNA aberrantly localized in the cytosol independent of its sequence context (3–5), and binding dsDNA promotes

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cGAS oligomerization and activation (3,6,7). In addition to playing a critical role in antiviral immune response, cGAS has also been shown to be involved in some other important biological processes such as macular degeneration (8), cellular senescence (9–11), myocardial infarction–related inflammation (12), and macrophage transformation (13). Activated cGAS catalyzes the formation of 2′3′-cGAMP, a cyclic dinucleotide (CDN) composed of adenosine and guanosine linked via two phosphodiester linkages. Apart from cGAMP, STING is also activated by CDNs such as cyclic di-AMP or cyclic di-GMP from bacteria (14).CDNs and 2′3′-cGAMP bind to the endoplasmic reticulum (ER)-localized STING, which promotes STING dimerization and translocation from the ER to perinuclear punctuate structures (14,15). During the trafficking process, STING recruits and activates TANK binding kinase 1 (TBK1), stimulating phosphorylation and nuclear translocation of the transcription factor interferon regulatory factor 3 (IRF3), and to a lesser extent nuclear factor-κB (NF-κB), which can also be activated by IκB kinase (IKK) (16,17), leading to the production of type 1 interferons (IFNs) and many other inflammatory cytokines (18) (Fig. 1). By binding to the IFN-α/β receptor on the cell membrane of target cells, IFNs promote the expression of proteins involved in inhibiting viral replication and thus enhances the protective defenses of the immune system (7,19). In addition to initiation of IFN signaling in cells in which it is produced by cGAS, there is some evidence showing that 2′3′-cGAMP is able to promote downstream signaling in neighboring cells via distinct mechanisms such as gap junction–, membrane fusion–, or viral particle–mediated transfer (20–22), thus mediating the cross talk between immune cells and their targeting cells. Intriguingly, activation of the cGAS-cGAMP-STING pathway could also be detected in nonimmune cells such as mouse embryonic fibroblasts and adipocytes (23,24), suggesting that activation of this pathway may have broader roles in addition to immune defense functions.

## Activation of the cGAS-cGAMP-STING Pathway by Self-DNA

In a healthy cell, host DNA normally resides in the nucleus or mitochondria. However, under certain pathophysiologic conditions such as DNA instability and/or mitochondrial stress, genomic DNA and/or mtDNA may be released into the cytoplasm, where it serves as a danger-associated molecular pattern to trigger immune responses. West et al. (23) found that, via heterozygosity of the mitochondrial transcription factor A (TFAM), disruption of mtDNA stability promoted mtDNA release into the cytosol, where it activated the cGAS-cGAMP-STING pathway and increased IFN gene expression. mtDNA-mediated activation of the cGAS-cGAMP-STING pathway is also observed by Bax/Bak-induced permeabilization of mitochondrial outer membrane (25,26). Besides mtDNA, recent studies show that the cGAS-cGAMP-STING pathway could also be activated by genomic DNA such as ruptured micronuclei and double-strand broken DNA of the primary nucleus caused by genomic instability and/or DNA damage (19,27–29). In addition to genomic DNA and mtDNA, phagocytic DNA inadequately digested in the lysosomes has been shown to activate the cGAS-cGAMP-STING pathway (7,19,30,31) (Fig. 1). These results demonstrate that self-DNA is an important source of sterile inflammatory response induction that has been widely studied in many of the autoimmune disease and cancers. These findings raise an interesting question as to whether self-DNA–induced sterile inflammation is associated with metabolic disorders.

## Activation of the cGAS-cGAMP-STING Pathway in Obesity-Induced Inflammation and Metabolic Diseases

Obesity is associated with various metabolic diseases such as type 2 diabetes, nonalcoholic fatty liver disease (NAFLD), cardiovascular disease, and many types of cancer. Numerous studies have shown that chronic sterile inflammation in adipose tissue plays a key role in mediating obesity-induced insulin resistance and its associated metabolic diseases (32,33). However, the precise mechanisms by which obesity causes inflammation remain to be fully elucidated.

During the past several years, evidence has accumulated to suggest an important role of the cGAS-cGAMP-STING pathway in regulating inflammation and energy homeostasis. The expression levels and/or activities of components in this signaling cascade, including cGAS, STING, and TBK1, are significantly upregulated under obesity conditions in mice (24,34,35). Activation of the cGAS-cGAMP-STING pathway in mouse adipose tissue could be triggered by high-fat diet (HFD)–induced mtDNA release, leading to an increase in chronic sterile inflammatory response (24). HFD-induced obesity and activation of the cGAS-cGAMP-STING pathway are prevented by adipose tissue–specific overexpression of disulfide bond A oxidoreductase-like protein (DsbA-L), a chaperone-like and mitochondrial localized protein whose expression in adipose tissue is greatly suppressed by obesity (36). Alternatively, knockout of DsbA-L in adipose tissue impaired mitochondrial function, increased mtDNA release, and activated the cGAS-cGAMP-STING pathway, leading to increased inflammation and exacerbated obesity-induced insulin resistance (24) (Fig. 2). These findings reveal that activation of the cGAS-cGAMP-STING pathway may mediate obesity-induced inflammation and metabolic dysfunction, beyond its well-characterized roles in innate immune surveillance. Consistent with this view, global knockout of the cGAS-cGAMP-STING downstream target TBK1 (37) or IRF3 (38), or pharmacological inhibition of IκB kinase ε (IKKε) and TBK1 by amlexanox, reduced body weight, enhanced insulin sensitivity, and improved glucose tolerance in obese mice and in a subset of patients with type 2 diabetes (34,39). However, it should be noted that while fat-specific knockout of TBK1 increased energy

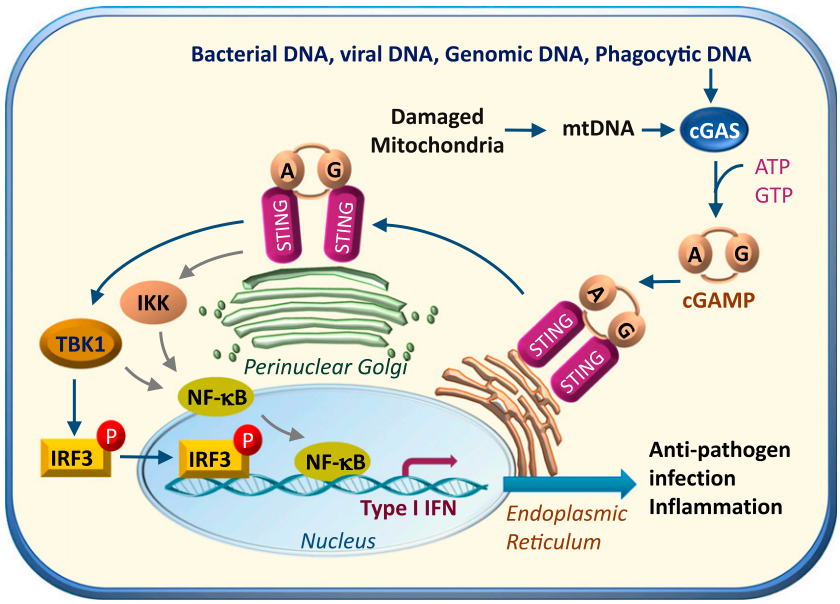


**Figure 1—** Activation and regulation of the cGAS-cGAMP-STING pathway in cells. The cGAS is activated by viral and bacterial DNA as well as mtDNA and phagocytosed DNA aberrantly localized in the cytosol. Activated cGAS uses ATP and GTP as substrates to catalyze the formation of the second messenger, cGAMP, which binds to STING localized on the ER membrane. The binding of cGAMP to STING promotes STING translocation to the Golgi apparatus. During the translocation, STING recruits and activates TBK1, which in turn catalyzes the phosphorylation and nuclear translocation of IRF3, and to a lesser extent NF-κB, which can also be activated by IKK, leading to increased synthesis of IFN and other inflammatory genes.

expenditure and attenuated HFD-induced obesity, it also exaggerated adipose tissue inflammation and insulin resistance, suggesting that TBK1 may have a feedback role in regulating obesity-induced inflammation (35) (Fig. 2). Indeed, activation of TBK1 has been found to reduce NF-κB activity and inflammation by promoting phosphorylation-dependent degradation of NF-κB–inducing kinase (NIK), an upstream kinase of IKKs (35). TBK1 has also been shown to attenuate cGAS-cGAMP-STING–mediated response by promoting STING ubiquitination and degradation (40) (Fig. 2). These findings explain the bidirectional roles of TBK1 in regulating inflammation (35). Nevertheless, it remains to be determined what role cGAS-cGAMP-STING signaling, which activates TBK1, may play in inflammation, insulin resistance, and energy expenditure in metabolic cells.

### The Potential Role of the cGAS-cGAMP-STING Pathway in NAFLD

In addition to mediating obesity-induced insulin resistance in adipose tissue, activation of the cGAS-cGAMP-STING pathway has also been implicated in other metabolic diseases including NAFLD. NAFLD is characterized by hepatic steatosis, which contributes to the development of nonalcoholic steatohepatitis (NASH), a potentially progressive liver disease that may lead to cirrhosis and hepatocellular carcinoma. There is some evidence suggesting that the innate immune response contributes to NAFLD and NASH (41–44). However, the underlying mechanisms by which the innate immune response promotes NALFD remain elusive. Luo et al. (42) and Yu et al. (45) recently independently found that activation of the liver cGAS-cGAMP-STING signaling pathway may mediate overnutrition-induced NAFLD and/or NASH. Indeed, STING levels were higher in liver tissues from NAFLD human patients compared with those without NAFLD. In addition, the mRNA levels of cGAS and STING are elevated in NASH mouse livers (42,46). Furthermore, the phosphorylation states of TBK1 and IRF3, two downstream targets of the cGAS-cGAMP-STING pathway, were significantly higher in livers of mice fed an HFD, which is coupled with NAFLD (42). Consistent with these findings, cGAS-cGAMP-STING–dependent activation of TBK1 in hepatocytes promotes the formation of insoluble p62/sequestosome 1 (SQSTM1) aggregates, a critical marker of NASH (47). On the other hand, STING deficiency attenuates steatosis, fibrosis, and inflammation in livers of mice fed with either methionine- and choline-deficient diet or HFD (42,45). Interestingly, both systemic or myeloid cell–specific knockout of STING increased resistance to HFD-induced or methionine- and choline-deficient diet–induced hepatic steatosis, inflammation, and/or fibrosis in mice (42,45). In addition, transplantation of bone marrow cells from control mice to STING knockout mice restored HFD-induced severity of steatosis and inflammation (42), suggesting that the improved metabolic phenotypes in the STING knockout mice were due to STING deficiency in liver-resident macrophages rather than in hepatocytes. These results are consistent with the finding that STING is not present in human and murine hepatocytes but is

expressed at high abundance in hepatic nonparenchymal cells (48). Indeed, there is some evidence showing that hepatocytes do not express STING (45,49) and that by facilitating hypoxia-induced autophagy in hepatocytes, cGAS protects the liver from ischemia-reperfusion injury via a STING-independent mechanism. The lack of STING in human hepatocytes also explains why hepatitis virus has adapted to specifically replicate in hepatocytes (48). It is well known that selective pressures in evolution promote the development of an effective immune surveillance system to ensure survival in the face of pathogen invasion. While at early stages infection initiates various biochemical processes such as glucose release from stored glycogen, glycogenolysis, and gluconeogenesis, the glucose synthesis ability of the infected body may be greatly impaired at later stages of overwhelming infection, leading to hypoglycemia (50). Because hypoglycemia is detrimental to an organism, in the frame of evolution there is no host survival advantage for chronic pathogen infection. Therefore, a successful immune response is often short-lived, resulting in the termination of the pathogen-induced response quickly to ensure an organism's survival. However, the lack of STING in hepatocytes results in type 1 IFN deficiency in response to hepatitis virus infection, which facilitates hepatitis viruses to escape from immune detection and causes not only acute but also chronic inflammation in the liver, leading to consequent hepatitis, cirrhosis, and hepatocellular carcinoma (48), which is often accompanied with metabolic dysfunction such as insulin resistance (51,52). Activation of the cGAS-STING pathway by overexpression of STING specifically in hepatocytes significantly suppressed the replication of hepatitis virus in vivo (48,53). Nevertheless, there are some reports showing that STING is present in hepatocytes and that knocking down either STING or IRF3 in hepatocytes alleviated lipid accumulation, hepatic inflammation, and apoptosis (54–56). These findings raise a possibility that some of the NAFLD phenotypes observed in the whole-body STING knockout mice may result from STING deficiency in the hepatocytes of the mice. Further studies are needed to clarify this discrepancy.

### The Cross Talk Between the cGAS-cGAMP-STING and the mTORC1 Signaling Pathways

The mechanistic target of rapamycin complex 1 (mTORC1) is a nutrient sensor that integrates energy, hormonal, metabolic, and nutritional inputs to regulate cellular metabolism, growth, and survival. Activation of the mTORC1 signaling pathway promotes anabolic processes such as protein, nucleotide, fatty acid, and lipid biosynthesis while inhibiting catabolic processes such as lipolysis and autophagy (57). Hasan et al. (58) recently found that chronic activation of the cGAS-cGAMP-STING signaling pathway is associated with reduced mTORC1 signaling in metabolically relevant tissues such as liver, fat, and skeletal muscle of the three-prime repair exonuclease 1 knockout (Trex1$^{-/-}$) mice, concurrently with increased inflammation and altered

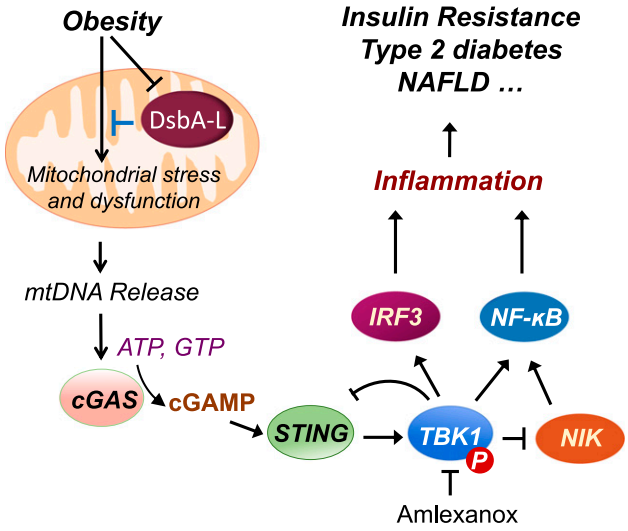


**Figure 2**—Activation of the cGAS-cGAMP-STING pathway mediates obesity-induced inflammation and metabolic disorders. Obesity reduces the expression levels of disulfide bond A oxidoreductase-like protein (DsbA-L) in adipose tissue, leading to mitochondrial stress and subsequent mtDNA release into the cytosol. Aberrant localization of mtDNA in the cytosol activates the cGAS-cGAMP-STING pathway, leading to enhanced inflammatory gene expression and insulin resistance. Phosphorylated and activated TBK1 exerts a feedback inhibitory role by promoting STING ubiquitination and degradation or stimulating phosphorylation-dependent degradation of NF-κB–inducing kinase (NIK), thus attenuating cGAS-cGAMP-STING–mediated inflammatory response.

metabolic phenotypes such as reduced adiposity and increased energy expenditure. Interestingly, STING deficiency in the Trex1$^{-/-}$ mice rescued both inflammatory and metabolic phenotypes, but IRF3 deficiency only rescued inflammation, suggesting that a component downstream of STING but upstream of IRF3 in the cGAS-cGAMP-STING pathway may play a role in regulating metabolism. Consistent with this view, they found that TBK1, the downstream target of STING, directly inhibited mTORC1 signaling by interacting with the mTORC1 complex (58) (Fig. 3). This result is in agreement with the findings of others that TBK1 inhibits mTORC1 activity in prostate cancer cells (59,60) and in an experimental autoimmune encephalomyelitis model (60). Nevertheless, one study reported that TBK1 may activate, rather than inhibit, mTORC1 through site-specific phosphorylation of mTOR at Ser$^{2159}$ in response to epidermal growth factor but not insulin treatment (61). On the other hand, there is some evidence showing that mTOR may inhibit the cGAS-cGAMP-STING antiviral pathway. Meade et al. (62) recently identified a cytoplasmically replicating poxviruses–encoded protein, F17, that binds and sequesters Raptor and Rictor. The binding of F17 to Raptor promotes mTORC1-mediated suppression of STING activity and IRF3 translocation to the nucleus. The binding of F17 to Rictor, on the other hand, facilitates mTORC2-mediated cGAS degradation. By disrupting the mTORC1-mTORC2 cross talk, F17 inhibits cGAS-cGAMP-STING signaling

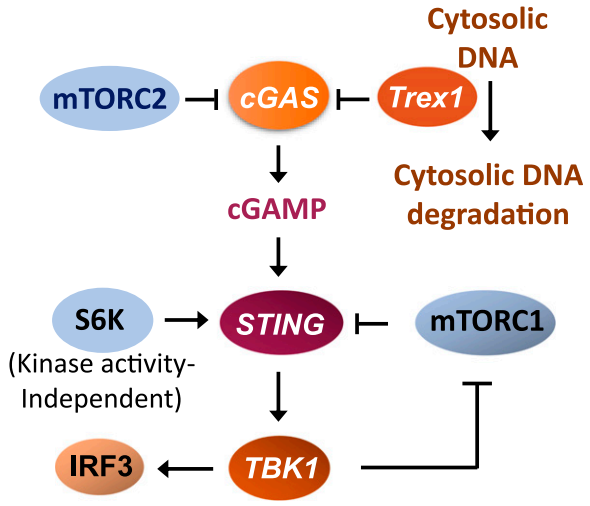


**Figure 3**—The interplay between the cGAS-cGAMP-STING pathway with mTORC1 signaling. Knockout of three-prime repair exonuclease 1 (Trex1), which degrades DNA in the cytosol, leads to the activation of the cGAS-cGAMP-STING pathway and suppression of the mTORC1 activity in mice. The cGAS-cGAMP-STING pathway may inhibit mTORC1 activity through a TBK1-dependent mechanism. Conversely, the cGAS-cGAMP-STING pathway may be inhibited by mTORC1-dependent suppression of STING activity and IRF3 translocation or by mTORC2-mediated cGAS degradation. Of note, the kinase domain but not the kinase function of ribosomal protein S6 kinase 1 (S6K1) is essential for S6K to interact with STING, which facilitates TBK1-mediated phosphorylation of STING and recruitment of IRF3 for antiviral immune responses.

and thus retains the benefits of mTOR-mediated stimulation of viral protein synthesis. Likewise, the mTOR downstream effector ribosomal protein S6 kinase 1 (S6K1) has been found to interact with STING in a cGAS-cGAMP–dependent manner, and the interaction promotes TBK1-mediated phosphorylation of STING and recruitment of IRF3 for antiviral immune responses (63). Of note, the interaction of S6K1 with STING is mediated by the kinase domain but not the kinase function of S6K1, suggesting a mTORC1-independent regulation of S6K1 on STING signaling (Fig. 3). Taken together, all these findings indicate a complex cross talk between the cGAS-cGAMP-STING and the mTORC1 signaling pathways. Further investigations will be needed to clarify these controversies and to elucidate the molecular details as well as the metabolic consequences of the cross talk between the cGAS-cGAMP-STING and the mTORC1 signaling pathways.

### The cGAS-cGAMP-STING Pathway and Autophagy/Mitophagy

In addition to cross talking to mTORC1, the cGAS-cGAMP-STING pathway has also been found to interact with the autophagy machinery in innate immune responses (Fig. 4). Autophagy exerts its quality control function by sequestering damaged organelles and protein aggregates and invading intracellular pathogens in the cytoplasm for lysosomal-mediated degradation (64). This programmed survival pathway also acts as a recycling system to maintain essential protein biosynthesis during stress conditions, such as nutrient insufficiency, growth factor depletion, and pathogen invasion (65). Thus, autophagy is important for the maintenance of the metabolic homeostasis of a cell, and its dysregulation might contribute to the development of metabolic disorders (66–68).

Autophagy is initiated with the activation of the ULK1 complex, which is inhibited by mTORC1 and promoted by nutrient deprivation and AMPK activation (67–69) (Fig. 4). Autophagy is also regulated by a multiprotein complex comprising beclin-1, a mammalian ortholog of the yeast autophagy-related gene 6 (Atg6), vacuolar protein sorting 34 (VPS34), and autophagy/beclin-1 regulator 1 (AMBRA1), which favors the nucleation of autophagosome precursors (67,70). Activation of the cGAS-cGAMP-STING pathway has been found to prompt ubiquitin-mediated autophagy that delivers bacteria to autophagosomes for degradation (71). Similarly, cGAS protects hepatocytes from ischemia-reperfusion injury–induced apoptosis in vivo and in vitro through an induction of autophagy in mouse hepatocytes (49). How cGAS stimulates autophagy in hepatocytes is currently unknown but appears to be mediated by a STING-independent mechanism (49). Interestingly, cGAS has been found to competitively bind beclin-1 to dissociate the negative autophagy factor rubicon from the beclin-1–phosphatidylinositol 3-kinase class III (PI3KC3) autophagy complex, leading to PI3KC3 activation and subsequent autophagy induction (72,73). This finding provides a possible explanation for the finding that cGAS promotes autophagy via a STING-independent mechanism. It is interesting to note that in addition to stimulating autophagy, the interaction between cGAS and beclin-1 negatively regulates cGAS enzyme activity in immune cells such as RAW264.7 and L929 cells, thus promoting cytosolic DNA degradation and preventing overactivation of the cGAS-cGAMP-STING pathway–mediated IFN responses and persistent immune stimulation (72). Activation of the cGAS-cGAMP-STING pathway also promotes an autophagy-dependent negative feedback regulation of STING, which is mediated by cGAMP-induced dephosphorylation of AMPK and activation of ULK1 that phosphorylates and promotes autophagosome-dependent degradation of STING (74) or by TBK1-p62/SQSTM1–dependent ubiquitination and degradation of STING (40), providing a mechanism to prevent the persistent transcription of innate immune genes (Fig. 4). However, a very recent study showed that upon binding cGAMP, STING translocated from the endoplasmic reticulum to the endoplasmic reticulum-Golgi intermediate compartment, which served as a membrane source for LC3 lipidation, leading to autophagosome formation and autophagy (75). This study reveals that the STING-induced activation of autophagy is mediated by a mechanism that is dependent on the Trp-Asp (W-D) repeat domain

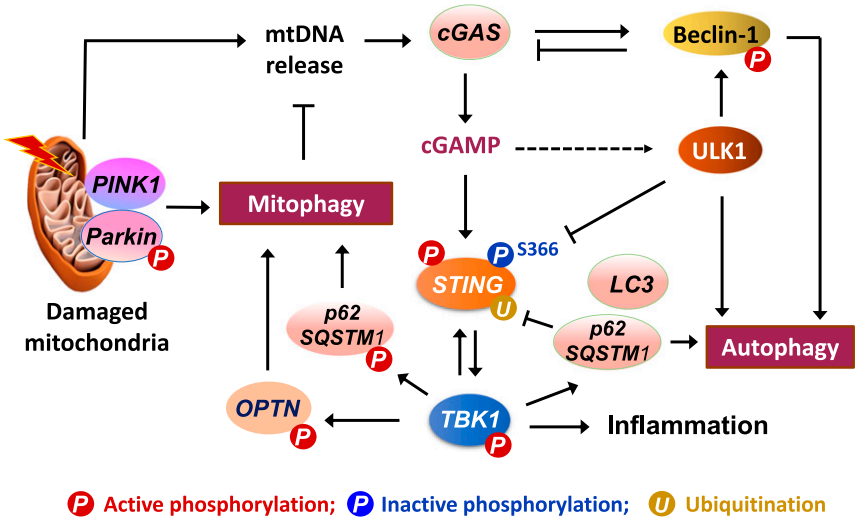


**Figure 4—**The cross talk between the cGAS-cGAMP-STING pathway and autophagy/mitophagy. Autophagy is initiated with the activation of ULK1 complex. ULK1-induced activation of beclin-1 complex favors the nucleation of autophagosome precursors and promotes autophagy. Mitophagy is a selective form of autophagy. Activation of the cGAS-cGAMP-STING pathway may stimulate autophagy via a cGAS/beclin-1 interaction–dependent mechanism. The cGAS-cGAMP-STING pathway also promotes autophagy/mitophagy by TBK1-dependent phosphorylation and activation of receptors OPTN and p62 (SQSTM). Alternatively, activation of the cGAS-cGAMP-STING pathway promotes an autophagy-dependent negative feedback regulation by *1*) the interaction of cGAS with beclin-1, which in turn inhibits cGAS activity; *2*) cGAMP-induced activation of ULK1, which promotes STING degradation by phosphorylation at $Ser^{366}$; and *3*) TBK1-p62/SQSTM1–dependent ubiquitination and degradation of STING. PINK/Parkin-induced mitophagy also restrains cGAS-cGAMP-STING signaling and innate immunity by mitophagy-mediated mtDNA clearance.

phosphoinositide-interacting protein (WIPI2) and autophagy-related gene 5 (ATG5), but independent of TBK1, ULK, or VPS34-beclin kinase complexes. Interestingly, p62/SQSTM1 has been shown to interact with mTOR and Raptor, which is critical for mTOR recruitment to lysosomes and for amino acid signaling–induced activation of S6K1 and 4EBP1 (76). However, it remains unknown whether the cGAS-cGAMP-STING signaling–induced and TBK1-mediated phosphorylation of p62/SQSTM1 plays a role in regulating mTORC1 signaling and function.

Mitophagy is a selective form of autophagy that mitigates inflammation by removing damaged mitochondria from cells (77). Mitochondrial damage induces mitophagy by promoting the accumulation of the ubiquitin kinase PINK1 on the outer membrane of the damaged mitochondria, which in turn phosphorylates Parkin at $Ser^{65}$, leading to the activation of this E3 ubiquitin ligase and subsequent degradation of ubiquitinated substrates (78). A recent study showed that Parkin and PINK deficiency promoted mtDNA release and activation of the cGAS-cGAMP-STING pathway in mouse heart tissue, leading to a strong inflammatory phenotype (77). These results support a role of PINK/Parkin-mediated mitophagy in restraining cGAS-cGAMP-STING signaling and innate immunity. By quantitative proteomics analysis, Richter et al. (79) recently found that the cGAS-cGAMP-STING downstream target TBK1 phosphorylated several mitophagy receptors such as optineurin (OPTN) and p62 (SQSTM) at their autophagy-relevant sites, which creates a signal loop amplifying mitophagy (Fig. 4). However, while these findings reveal a link between the cGAS-cGAMP-STING pathway and autophagy/mitophagy, the detailed biochemical mechanism underlying the link remains largely elusive, especially in metabolic tissues. Seeking answers to these questions would be an attractive subject for further investigation.

### The cGAS-cGAMP-STING Signaling and Apoptosis

Apoptosis is a programmed cell death process that provides a mechanism to maintain organismal homeostasis (80). Apoptosis is regulated by prodeath proteins such as Bak and Bax and prosurvival proteins such as BCL-2 and BCL-XL. Bak/Bax activation promotes mitochondrial outer-membrane permeabilization and the release of apoptotic proteins such as cytochrome c to the cytosol, leading to further activation of the downstream pathway of intrinsic apoptosis through initiator and executioner caspases cascade (81) (Fig. 5). Activation of caspases, which is a hallmark of apoptosis, has been found to not only promote cell death but also prevent dying cells from triggering a host immune response (82). However, while apoptosis has long been known as an immunologically silent form of cell death, the molecular basis underlying the suppression of immune responses remains unknown. Several recent studies suggest that caspase-mediated inhibition of the cGAS-cGAMP-STING signaling pathway may contribute to the silencing of immune process in apoptotic cells. In agreement with this, TBK1 phosphorylation and IFNα-stimulated gene expression are increased in caspase-9 knockout or caspase-3/-7 double knockout mice and cells

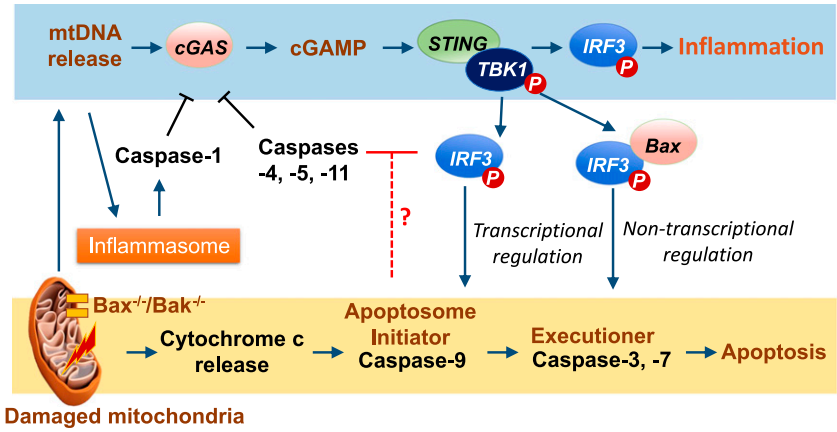


**Figure 5**—The association of cGAS-cGAMP-STING signaling with apoptosis. The activation of prodeath proteins such as Bax/Bak promotes mitochondrial outer-membrane permeabilization and the release of cytochrome c to the cytosol, leading to activation of intrinsic apoptosis through initiator and executioner caspases cascade. Defects in apoptosis by knocking out caspase-9 or caspase-3/-7 lead to constitutive activation of the cGAS-cGAMP-STING pathway; however, the precise mechanisms by which caspase-induced apoptosis inhibits innate immune remain unknown. Inflammatory caspases including caspase-1, which can be activated by mtDNA release–induced formation of inflammasome, or caspase-4, -5, and -11 cleave cGAS, thus preventing the activation of immune response. Alternatively, activation of the cGAS-cGAMP-STING pathway promotes apoptosis via both transcriptional and nontranscriptional programs in a TBK1-IRF3–dependent manner.

(25). Constitutive activation of the type I IFN response was also observed in caspase-9–deficient mouse embryonic fibroblasts (26). In addition, inhibition of caspases led to increased phosphorylation of TBK1 and IRF3 in Bax/Bak-sufficient cells but not in Bax/Bak knockout cells. Furthermore, the caspase deficiency–induced IFNβ response was prevented by knocking out cGAS or STING (25). These findings suggest that apoptosis may suppress immune responses by inhibiting the cGAS-cGAMP-STING pathway. However, the precise biochemical mechanism(s) by which caspases negatively regulate the cGAS-cGAMP-STING pathway remains unclear but could result from multiple redundant processes such as attenuated gene expression, cleavage and inactivation of a component or components of the type I IFN production pathway, and caspase-mediated degradation of mtDNA, thereby disrupting its interaction with cGAS, thus preventing the activation of the cGAS-cGAMP-STING signaling pathway and its downstream IFN action (26). Consistent with this, Wang et al. (83) found that cGAS could be cleaved by several inflammatory caspases including caspase-1, which can be activated by mtDNA release–induced formation of inflammasome, or by caspase-4, -5, and -11. Alternatively, activation of the cGAS-cGAMP-STING pathway may promote apoptosis via both transcriptional and nontranscriptional mechanisms (84,85). It has been shown that STING activation in T cells induces apoptosis through an IRF3- and p53-mediated transcriptional proapoptotic program (86). A proapoptotic but transcription-independent role of STING is observed in hepatocytes that is mediated by the association of IRF3 with the proapoptotic molecule Bax/Bak, which contributes to alcoholic liver disease (55). The proapoptotic role of STING was also found in other cells such as B cells and endothelial cells (87,88). Collectively, these findings demonstrate a complicated cross talk between cGAS-cGAMP-STING signaling and apoptosis. Given the importance of apoptosis in regulating metabolic homeostasis, it would be of great interest to determine the functional roles of the cross talk between cGAS-cGAMP-STING signaling and apoptosis in metabolic tissues.

## Concluding Remarks

Inflammation is now clearly recognized as a major risk factor for obesity-induced metabolic disorders. Suppressing inflammatory pathways, therefore, holds promise for developing effective therapeutic treatment of obesity-related diseases. However, identification of pharmacological targets to suppress inflammation is usually a challenge, requiring better understanding of the mechanisms underlying obesity-induced inflammation. The identification of the cGAS-cGAMP-STING pathway as a key player in mediating obesity-induced chronic low-grade inflammation has pointed out an exciting new direction to elucidate the mechanism underlying obesity-induced metabolic diseases and to develop potential therapeutic strategies to improve metabolic homeostasis. However, a number of important questions remain to be answered.

First, while the pivotal roles of the cGAS-cGAMP-STING pathway in immune defense against various microbial pathogens have been extensively studied (3–5), its function in non-immune cells remains largely unexplored. The findings that the cGAS-cGAMP-STING pathway components such as cGAS, STING, and TBK1 are highly expressed in adipocytes and that the expression levels of these molecules are stimulated under obesity conditions (24) raise a possibility that activation of this pathway may play an important role in metabolic diseases. However, it should be acknowledged that HFD feeding activates the cGAS-cGAMP-STING pathway not only in adipocytes but

also in macrophages (24,42), the predominant proinflammatory immune cell type in obese adipose tissue (89), suggesting that activation of the cGAS-cGAMP-STING pathway in adipose tissue–resident macrophages may make a significant contribution to the deteriorated metabolic phenotypes of the obese mice. Further studies will be warranted to dissect the relative contribution of the cGAS-cGAMP-STING pathway in metabolic relevant cells, such as such hepatocytes and adipocytes, and tissue-resident immune cells and the potential cross talk between these cells triggered by cGAS-cGAMP-STING pathway activation.

It is interesting to note that the function of cGAS and STING is regulated by mTOR complexes and vice versa (63,74) (Fig. 3), suggesting that activation of the cGAS-cGAMP-STING pathway may be modulated by environmental inputs such as cellular nutrient status and/or growth factors' stimulation. However, the underlying mechanism by which DNA-induced activation of the cGAS-cGAMP-STING pathway is moderated by environmental changes remains unexplored. In addition, given that mTORC1 plays a pivotal role in regulating cell metabolism and energy homeostasis, it is possible that activation of the cGAS-cGAMP-STING pathway may mediate some of the multifaceted roles of mTORC1 signaling pathway. Interestingly, activation of TBK1 has been shown to inhibit mTORC1 activity (58), suggesting a potential negative regulation of mTORC1 signaling by activation of the cGAS-cGAMP-STING pathway. Further studies will be needed to elucidate the precise mechanism underlying the cross talk between these two signaling pathways and the physiological roles of the interaction. In addition to the mTORC1 signaling pathway, available evidence suggests that the cGAS-cGAMP-STING pathway also cross talks to both autophagy and apoptosis (Figs. 4 and 5). Autophagy and apoptosis regulate the turnover of cellular organelles and cells within organisms, and their interaction is highly context dependent and in most of cases mutually inhibitory (90). The identification of the cGAS-cGAMP-STING pathway linking to both autophagy and apoptosis suggests an important new layer of regulation of these distinct mechanisms for the control of cell homeostasis. However, an integrated understanding of the interplay between the cGAS-cGAMP-STING and these cellular pathways remains largely unclear. It is also unknown when and which inputs to the network are dominant and how this depends on the physiological or pathophysiological context. Answers to these questions will likely require both deeper biochemical and physiological studies of the interaction both in vitro and with tissue-specific transgenic and/or knockout mouse models that enable more specific perturbation and monitoring of these pathways in vivo.

Lastly, it remains to be established whether and how targeting the cGAS-cGAMP-STING pathway is a suitable strategy to treat metabolic diseases. Given that the cGAS-cGAMP-STING pathway is activated by mitochondrial stress under obesity conditions, it is tempting to speculate that at least a part of the effects of increased inflammation may be due to activation of the cGAS-cGAMP-STING pathway. In fact, much progress has been made on the development of small-molecule inhibitors targeting components in the cGAS-cGAMP-STING pathway over the past several years. As of now, several cGAS inhibitors have been reported. By in silico screening of drug libraries using mouse cGAS/DNA target (PDB 4LEZ), An et al. (91) recently identified hydroxychloroquine, quinacrine, and 9-amino-6-chloro-2-methoxyacridine as potential cGAS inhibitors. These molecules do not bind to the active site of cGAS but are instead found to localize to the minor groove of DNA between the cGAS/DNA interface (91). RU.521 and RU.365, however, are found to inhibit cGAS by binding at the cGAS active site (92). Wang et al. (93) showed that suramin, a drug used clinically for the treatment of African sleeping sickness (94), binds to the DNA binding site of cGAS and inhibits cGAS activity by disrupting dsDNA/cGAS binding. In addition to targeting cGAS, several small-molecule inhibitors of STING have also been reported. By a cell-based chemical screen, Haag et al. (95) recently identified two nitrofuran derivatives—C-178 and C-176—that strongly reduced STING-mediated, but not RIG-I– or TBK1-mediated, IFNβ reporter activity. Excitingly, they found that these derivatives reduce STING-mediated inflammatory cytokine production in both human and mouse cells and attenuate pathological features of autoinflammatory disease in mice (95). Very recently, Dai et al. (96) reported that aspirin, a nonsteroidal anti-inflammatory drug, can directly bind and enforce the acetylation of cGAS, leading to a robust inhibition of cGAS enzymatic activity and self-DNA–induced immune response in both Aicardi-Goutières syndrome patient cells and a mouse model of Aicardi-Goutières syndrome. These results provide proof of concept that targeting the cGAS-cGAMP-STING pathway may be efficacious in the treatment of inflammatory diseases, which opens new avenues for developing novel therapies for inflammation-related metabolic diseases. Future work on the molecular details of the regulation and network of the cGAS-cGAMP-STING pathway and its tissue-specific function should enable the rational targeting of this signaling to unravel the full therapeutic potential of this extraordinary pathway in metabolism and relevant biological functions.

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