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**Title:** Alternative Pathways Driven by STING: from Innate Immunity to Lipid Metabolism

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**Abstract**

The Stimulator of Interferon Genes (STING) is a major adaptor protein that is central to the initiation of type I interferon responses and proinflammatory signalling. STING-dependent signalling is triggered by the presence of cytosolic nucleic acids that are generated following pathogen infection or cellular stress. Beyond this central role in controlling immune responses through the production of cytokines and chemokines, recent reports have uncovered inflammation-independent STING functions. Amongst these, a rapidly growing body of evidence demonstrates a key role of STING in controlling metabolic pathways at several levels. Since immunity and metabolic homeostasis are tightly interconnected, these findings deepen our understanding of the involvement of STING in human pathologies. Here, we discuss these findings and reflect on their impact on our current understanding of how nucleic acid immunity controls homeostasis and promotes pathological outcomes.

**Keywords:** STING, Inflammation, Innate immunity, Lipid metabolism, metabolism

## ***Introduction***

Metabolic and immune homeostasis are tightly linked. Indeed, cytokine production in the course of immune responses can induce systemic metabolic alterations, while feeding behaviors affect immuno-metabolism. Metabolic reprogramming is also required for immune cell activation. The best example of the interconnection between immune cell function and global metabolic homeostasis can be observed during obesity. Obese patients present massive infiltration of active immune cells in the adipose tissue [1], leading to the overproduction of cytokines and chemokines [2] that constitutes the hallmark of chronic low-grade inflammation. Tumor necrosis factor-alpha (TNF- $\alpha$ ) was the first cytokine identified to be secreted by the adipose tissue in obese state, a factor shown to be essential for the development of obesity-related insulin resistance [3, 4]. It was later shown that TNF- $\alpha$  impairs insulin signaling by targeting the insulin receptor substrate-1 (IRS-1) [5, 6]. Following these studies showing the importance of TNF- $\alpha$  in mediating metabolic disease in obesity, multiple other cytokines and hormones were found to play a similar role [7]. While initial work highlighted the contribution of immune cells to tissue inflammation on insulin resistance, recent studies demonstrate that metabolism can also impact immune cells. Indeed, metabolic dysregulation, in particular lipid accumulation, in immune cells also participate in obesity-induced pathogenesis [7].

Immuno-metabolism is an emerging field that investigates the interplay between immunological and metabolic regulations. Six major metabolic pathways have been studied in immune cells in details [8]. Among those pathways, glycolysis plays a major role. Indeed, glycolysis is considered as a hallmark of metabolic changes in most activated immune cells in response to stimulation via pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) receptors, cytokine receptors or antigen receptors. For example, the activation of macrophages resulting from the interaction of the bacterial cell wall component lipopolysaccharide (LPS) with Toll-like receptor 4 (TLR4) constitutes a major pathway for the initiation of innate immune responses and the development of inflammation. Activation of TLR4 leads to a metabolic switch from oxidative phosphorylation to glycolysis [9]. Glycolysis is induced through the stabilization of Hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) a transcription factor that is crucial for the induction of several enzymes involved in glycolysis and the production of the cytokine IL1 $\beta$  [10].

Recent studies have unveiled that innate immune pathways are also key players in the maintenance of metabolic homeostasis. Within the present review, we focus on the role played by the pathways involved in the detection of cytosolic nucleic acids in the regulation of metabolic homeostasis. In particular the stimulator of interferon genes (STING) adaptor protein has been shown to play a major role in integrating both inflammatory and metabolic input to coordinate homeostasis. STING was initially identified as a central hub on which cytosolic nucleic acid detection mechanisms converge to promote transcriptional reprogramming leading to the production of inflammatory cytokines, chemokines and type I Interferons (IFNs). As such, dysregulation of STING signaling has a broad impact on human health and is associated to a wide range of inflammation-related pathologies. Several non-canonical functions have subsequently been reported, enlarging the range of implications of STING. In view of recent evolutionary studies on this pathway, we speculate on the emergence of both functions and their role throughout evolution.

### ***1. STING Signaling & Regulation***

The STING protein is a central hub of nucleic acid-associated inflammatory responses, on which several receptors have been shown to converge. STING expression and activation are therefore fine-tuned in order to avoid detrimental overstimulation (Figure 1).

### 1.1. The cGAS-STING pathway: an overview

Amongst major upstream activators of STING is the Cyclic GMP-AMP synthase (**cGAS**) receptor. cGAS is a major cytosolic DNA sensor that triggers innate immune responses [11] via STING [12]. Upon binding to nucleic acids, cGAS catalyzes the production of the 2'3'-cyclic guanosine monophosphate–adenosine monophosphate (2'3'-cGAMP) cyclic dinucleotide (CDN). The preponderant role of 2'3'-cGAMP synthesis by cGAS after DNA sensing is supported by the incapacity of catalytically inactive mutants of cGAS to induce IFN response, despite their ability to bind DNA [13]. Solving the 3D structure of STING alone and in association with 2'3'-cGAMP revealed a butterfly-shaped dimer, that upon binding 2'3'-cGAMP in the cyclic dinucleotide (CDN) binding pocket, undergoes a rotation of both monomers towards the ligand-binding pocket [14, 15]. In addition to the closure of the CDN-binding pocket, binding of 2'3'-cGAMP induces a 180° rotation of the ligand-binding-domain dimer, leading to the formation of the STING tetramer and higher-order oligomer [16]. This study confirmed older reports in which STING aggregation was shown to be necessary for IFN induction [17].

Additional CDN ligands can activate STING: bacterial CDN including: c-di-GMP/CDG (cyclic-di-guanosine monophosphate), c-di-AMP/CDA (cyclic-di-adenosine monophosphate) and 3'3'-cGAMP [14, 18, 19]. Recently, Ap4A (diadenosine tetraphosphate) an endogenous dinucleotide produced by the protein Lysyl t-RNA synthetase (LysRS) was shown to compete with 2'3'-cGAMP for STING binding-pocket leading to an increase in the threshold of CDN concentration required to induce a STING-dependent IFNs response [20]. Interestingly, while STING-mediated IFN signaling is not conserved throughout evolution, binding of CDN ligands is a largely conserved function of STING in all metazoans and so is the cGAS-STING signaling pathway which existed more than 500 million years ago in ancestral metazoans [21]. In fact, IFNs signaling likely originated much later than the evolution of CDN-STING interaction. Upon ligand binding in the cytosol, STING can trigger two inflammatory pathways - the nuclear factor kappa B (NF-κB) [22, 23] and interferon-regulatory factor 3 (IRF3) [24] signaling cascades, and a cGAMP-induced non-canonical autophagy pathway [25], which are all conserved in ancient metazoans [26], implying that their link with the cGAS-STING pathway predates the evolution of IFN-based immunity.

Another key parameter of STING activation is its subcellular localization. In basal (unstimulated) conditions, STING is an endoplasmic reticulum (ER)-associated membrane protein. After CDN binding, STING translocates from the ER to perinuclear compartments including the Golgi network, endosomes, and autophagy-related compartments [12, 27]. Binding of 2'3'-cGAMP to STING promotes autoactivation of TANK binding kinase (TBK1) by its *trans* phosphorylation by an adjacent TBK1 molecule. ER retention of STING and blockade of ER-to-ER-Golgi-intermediate-compartment (ERGIC)/Golgi-trafficking mechanism of STING abolishes TBK1 phosphorylation which is necessary for IFN response induction [28, 29]. Moreover, STING signaling requires phosphorylation of its C-terminal tail by activated TBK1 on Ser366 site (Ser365 in mouse), which occurs only after STING is activated [30]. However, none of the available structures of STING allow visualization of the C-terminal tail. Recent mutational analyses validate that oligomerization of both STING and TBK1 are necessary to allow STING phosphorylation by TBK1 [31].

Phosphorylation of STING by TBK1 recruits IRF3, thereby facilitating IRF3 phosphorylation by TBK1 [24]. This process leads to dimerization of active IRF3 which translocates to the nucleus and induces transcription of IFN-β and other related genes [22, 30, 32]. TBK1 was recently identified as an IκB kinase (IKK)-related kinase; TBK1 controls the activation of NF-κB through the IKKαβ phosphorylation, in response to STING activation. Finally, STING was shown to be able to form phase-separated condensates isolating STING/TBK1 complex from IRF3 thus limiting the type I IFN response. This study sheds a new light on STING regulation, inferring that STING could act as a cGAMP sponge, sequestering

cGAMP in STING biocondensates, in order to prevent innate immunity from overactivation [33]. Such sponging-off of cGAMP could also limit the potential additional biological impacts of cGAMP molecules that are just starting to emerge [34, 35].

While STING harbors a transmembrane domain, ensuring its anchoring to the membrane of the endoplasmic reticulum, palmitoylation of two cysteine residues (Cys88 and Cys91) in human STING are important for its activation and play an essential role in IFN response induction. Disruption of STING palmitoylation due to modification of Cys88/91 through nitro-alkylation by naturally formed nitro fatty acids was shown to inhibit STING signaling [36]. A high-throughput screening study has identified potent STING antagonists which also act through covalently targeting the Cys91 residue and thereby blocking palmitoylation of STING [37]. Thus, STING palmitoylation is essential for STING trafficking and clustering at the Golgi apparatus [38]. It was suggested that this palmitoylation process, via the action of the protein palmitoyl transferases Asp-His-His-Cys (DHHC3, DHHC7, and DHHC15), enhances STING activation by contributing to the oligomer interface [16, 38]. This lipid-based posttranslational modification is essential in STING signaling and disturbing Golgi lipid raft composition alters STING dependent inflammatory responses [38], underscoring the close relationship between lipid metabolism and STING-dependent inflammatory responses. Lipid raft composition can be modified under certain circumstances such as diseases [39, 40] or certain diets e.g. Omega-3 enriched diet [41]; in those contexts, STING-dependent signaling could be either more or less easy to trigger, impacting response to pathogenic or cytosolic nucleic acid accumulation.

## 1.2. STING gene and protein: evolutionary conservation

STING, also known as MITA [42], MPYS [43], TMEM173 and ERIS [44] is encoded by the *TMEM173* gene. The human STING allele is composed of eight exons and seven introns (~7kb-long gene at 5q31.2) and encodes a 379 amino acid protein. STING comprises four transmembrane (TM) helical regions in the N-terminus and a large cytoplasmic domain in the C-terminus [12]. This C-terminal domain (CTD) mediates dimerization, CDN ligand-binding and protein-protein interactions, whereas the TM domains govern intracellular localization [24]. STING is an ancient protein, found to be expressed in bacteria [45]. Its structure has significantly changed and evolved from unicellular organisms to vertebrates [46]. Before the existence of IFNs system in vertebrates, STING was already playing a central role in anti-pathogen immunity in unicellular protists [47] and invertebrates species [48, 49]. In these organisms STING executes its immune function by inducing autophagy and activation of NF- $\kappa$ B signaling (a homolog of NF- $\kappa$ B in protists) [50], the two downstream pathways thought to be associated with ancestral STING function. At present, there are indications that the role of STING in metabolic regulation is conserved in mice [35], human [35] and drosophila [51], although the mechanism through which this is achieved in drosophila remains elusive.

Interestingly, Human populations are highly heterogeneous for the *TMEM173* gene [52]. Common *STING* haplotypes are R232 (WT), HAQ (composed of three single-nucleotide polymorphisms (SNPs): R71H-G230A-R293Q), AQ (G230A-R293Q), Q293 (R293Q) and H232 (R232H) [53, 54]. The R232 STING haplotype, considered as “wild type”, is the most prevalent human STING isoform, occurring naturally in 60% of the human population. R232/R232 is the dominant *TMEM173* genotype in Europeans, while R232/HAQ is the most common *TMEM173* genotype in East Asians. Overall, ~30% of East Asians and ~10% of Europeans are HAQ/HAQ, HAQ/H232, or H232/H232. Finally, the Q293 allele is predominantly present within the African subpopulation and ~4% of Africans are AQ/AQ, which is absent in other ethnic populations [55]. Confoundingly, recent studies have suggested that STING HAQ is a loss-of-function *TMEM173* allele, since as HAQ/HAQ cells express low STING protein and decreased *TMEM173* mRNA level compared to R232/R232 cells. Indeed, knock-in mice

expressing a mouse equivalent of the HAQ allele (mHAQ) present decreased STING protein in most immune cells and lung tissues. These mice also fail to respond to CDNs stimulation *in vitro* and *in vivo* [55]. Whereas other alleles show decreased stimulation of STING by CDNs, G230A STING respond to lower concentrations of c-di-GMP meaning that the G230A mutation increases the affinity of c-di-GMP binding [54]. Such diversity of haplotype in the human population is intriguing. Fixation of a haplotype in a particular ethnic population is expected to confer an advantage. As such, the HAQ haplotype, which leads to decreased levels of STING protein should present a benefit.

Several STING isoforms, in addition to the full-length STING protein (coined: STING- $\alpha$ ), have been described, including the MITA-related protein (MRP) and STING- $\beta$ . Both isoforms act as dominant negative regulators of STING function. The MRP isoform results from alternative splicing and lacks exon 7. MRP was shown to inhibit IRF3 activation, by disrupting STING-TBK1 interaction, while still permitting NF- $\kappa$ B activation [56]. Transcription of STING- $\beta$  is driven by an alternative promoter and starts with 25 amino acids from intron 5, followed by exons 6, 7, and 8, resulting in a 231 amino acids-long protein that suppresses both IRF3 and NF- $\kappa$ B activation by cGAMP and other stimuli [57]. Recently another spliced STING isoform was identified, this isoform is localized at the plasma membrane (pmSTING), its C-terminus is localized outside the cell and allows sensing of extracellular cGAMP [58]. The prevalence in human populations and conservation of these STING isoforms together with their impact on non-canonical STING functions are unexplored as of now.

Finally, epigenetic, transcriptional and post-transcriptional regulatory mechanisms can affect STING expression. STING expression is repressed in many cancer cell lines [59]. Epigenetic silencing enzymes such as DNA methyltransferase (DNMT1) and enhancer of zeste homolog 2 (EZH2) were shown to be hyperactive in some cancers in which they silence STING expression leading to a decrease of dsDNA response [60]. The processing body-associated protein LSM14A favors nuclear STING mRNA precursor processing in dendritic cells [61]. STING mRNA stability can also be regulated by the transcription factor Nrf2 leading to decreased STING protein expression [62]. Such heterogeneity in STING levels has also been reported in healthy tissues as well, for instance hepatocytes in the liver do not express STING, a property exploited by Hepatitis B virus (HBV) which has exclusively adapted to replicate in hepatocytes [63].

### 1.3. Alternative STING-dependent DNA sensors:

The cGAS-STING axis has been in the spotlight in recent years, notably with cGAS- and STING-deficient mice displaying ablated IFN responses upon stimulation with dsDNA. Yet, there is mounting evidence for the fact that DNA sensing mechanisms are governed by species specific alternative pathways. For instance, in humans a STING-independent DNA sensing pathway (SIDSP) is mediated by the DNA damage response protein DNA-dependent protein kinase (DNA-PK), a pathway shown to be not functional in mice [64]. This supports the fact that roles and implications of alternative receptors and their crosstalk between each other, should be re-evaluated in human cells and samples. Furthermore, STING was shown to regulate activation of the NLRP3 inflammasome, notably through enabling the recruitment of NLRP3 to the endoplasmic reticulum [65]. Such co-regulation has also been reported between STING and major players in the DNA damage responses, which is another context where detection of abnormal DNAs is paramount. For insight into the role of such pathways in triggering type I IFN responses, see [66].

In addition to these, DEAD-box helicase 41 (DDX41) [67], Interferon  $\gamma$ -Inducible Protein (IFI16) [68, 69], DLM-1/ZBP1 (DAI) [70] and LSM14A were also shown to be able to detect double stranded DNAs (dsDNAs) and promote STING-TBK1-IRF3 or NF- $\kappa$ B activation. Interestingly, although converging on STING, they have been shown to promote differential signaling output and have very different modes of action. DDX41 was identified in myeloid

dendritic cells, as an intracellular DNA sensor [67]. It was shown to bind DNA and co-localizes with STING in the cytoplasm. DDX41 was found to be bound to STING even in the absence of cytoplasmic DNA challenge, suggesting an important role in initial sensing of exogenous DNA and in triggering an early burst of the type I IFN response. IFI16 was described as another DNA sensor that associates with viral DNAs, recruits STING and activates the innate immune response [69]. Overexpression of DAI was shown to increase intracellular pathogenic DNAs-induced type I IFN production [70]. However, DAI-deficient mice or cells display normal type I IFN responses stimulated by dsDNA [71], suggesting that DAI may be dispensable for cytosolic DNA recognition. DAI was also suggested to exert its DNA sensing role in a cell type specific manner [72]. LSM14A, a member of the LSM family proteins involved in RNA processing in the processing bodies, was found to bind to synthetic or viral RNA and DNA and mediate IRF3 activation and IFN- $\beta$  induction [73] LSM14A responds rapidly to exogenous nucleic acids and leads to early-phase production of IFNs. When LSM14A binds to DNA it induces IRF3 activation via STING recruitment.

Finally, although the canonical role of STING in mammals in association with cGAS, is to sense cytosolic DNA species [74] and RNA:DNA hybrids [20], STING has been implicated in RNA virus-induced cytokine production via STING interaction with retinoic acid-inducible gene I (RIG-I) and mitochondrial antiviral-signaling protein (MAVS) [12, 42], which are key components of the RNA sensing pathway. Several points of cross-talk between RIG-I-MAVS and cGAS-STING nucleic acid sensing pathways have been reported, they are thought to help amplify the innate antiviral responses against both RNA and DNA viral pathogens [75]. In *Drosophila*, two cGAS-like receptors (cGLRs), cGLR1 and cGLR2 have been identified which can trigger STING- and NF- $\kappa$ B-dependent signaling by producing 2'3'-cGAMP or 3'2'-cGAMP in response to infection with both RNA and DNA viruses. cGLR1 recognizes dsRNA, while the stimulus of cGLR2 is not yet known [76]. Altogether, this underscores the role of STING as a pivotal point around which a diverse yet interlinked set of nucleic acid sensing pathways operate.

#### 1.4. Regulation of STING:

Several mechanisms operating at different levels, from protein regulators (Table I) to post-translational modifications, have been reported to regulate STING positively or negatively.

Although the exit of STING from the ER is a rate-limiting step in the cGAS-STING signaling pathway, a mechanistic understanding of this step was rather limited for a very long time. Recently, the STING1 ER Exit Protein (STEEP) was identified as a crucial positive regulator of STING signaling which induces ER membrane curvature and COPII-dependent ER-to-Golgi trafficking of STING [77]. Optimal function of STING also requires direct interaction with other positive regulators such as, the cytosolic protein TIR-domain-containing adapter-inducing interferon- $\beta$  (TRIF). TRIF promotes STING dimerization and intermembrane translocation [78]. A tripartite complex between STING-TBK1 and S6 kinase (S6K1), a metabolic checkpoint kinase involved in mTOR pathway regulation, was shown to be necessary for the activation of IRF3 but not NF- $\kappa$ B [79]. ER-associated proteins with palmitoyltransferase activity namely Zinc Finger DHHC-Type Containing 1 (ZDHHC1) and ZDHHC11, were found to be associated with STING, favoring its dimerization and helping the recruitment of the downstream signaling components TBK1 and IRF3 [80, 81].

Interestingly, amongst the direct negative regulators of STING are other nucleic acid receptors. For example, the NOD-like receptors NLR family CARD domain-containing protein 3 (NLRC3), and NLR Family Member X1 (NLRX1) that normally detect intracellular viral DNA and RNA respectively, both bind to STING through their nucleotide binding domains (NBD), sequestering STING at the ER and preventing its interaction with TBK-1, thus attenuating

STING signaling [82, 83]. Protein phosphatase Mg<sup>2+</sup>/Mn<sup>2+</sup> dependent 1A (PPM1A), a member of the PP2C family of Ser/Thr protein phosphatases, was identified as a STING-interacting protein. PPM1A dephosphorylates STING and antagonize TBK1 action on STING and therefore decreases STING aggregation [17]. The IFN-inducible protein interferon-stimulated gene 56 (ISG56) acts as a negative feedback regulator by disrupting the interactions between STING and TBK1 [84]. Recent works have also identified the Ca<sup>2+</sup> sensor stromal interaction molecule 1 (STIM1) as a critical STING binding partner, acting as an anchor and responsible for its ER retention, thus preventing spontaneous activation of dominant STING mutants that cause autoinflammatory diseases [85]. Niemann-Pick type C1 (NPC1), a lysosomal membrane protein, was reported to interact with STING and participate in its trafficking to the lysosome for degradation in both murine and human cells. Knocking out NPC1 activates STING signaling and IFN production even in the absence of cGAMP [86]. Another important negative regulator of STING is the Nuclear factor erythroid 2-related factor 2 (Nrf2) which when activated, diminishes expression of STING and its responsiveness to agonists. It has been demonstrated that Nrf2 controls STING expression by reducing the stability of STING mRNA [62]. The regulation of STING by Nrf2 is thought to be associated with the latter's role in promoting metabolic reprogramming, a topic which has been discussed in the following sections.

STING activation is also regulated by a plethora of post-translational modifications (PTMs) including ubiquitylation, SUMOylation, phosphorylation, and palmitoylation showing the importance of its fine-tuned regulation to maintain tight control of immune responses and prevent autoimmune diseases. STING can be modified by different E3 ubiquitin ligases catalysing the ubiquitination process. Tripartite Motif containing protein 32 (TRIM32) and TRIM56 have been implicated in K63-linked ubiquitination of STING promoting type I IFN induction [87, 88]. TRIM29, TRIM30 $\alpha$  were reported to induce K48-linked ubiquitination leading to STING degradation through a proteasome-dependent pathway [89-91]. TRIM38 on the other hand, sumoylates STING during the early phase of viral infection to promote its activation and increase its stability [92]. Ring finger protein 26 (RNF26) is an E3 ubiquitin-protein ligase, that promotes K11-linked polyubiquitination, while RNF5 promotes a K48-linked polyubiquitination on the same residue. RNF26 protect STING from RNF5-mediated ubiquitination and degradation after viral infection [93]. The Autocrine motility factor receptor (AMRF), an ER protein, is recruited on STING by Insulin-induced gene 1 (INSIG1) to help catalyze the K27-linked polyubiquitination of STING. This modification acts as an anchor on the STING platform for TBK1 recruitment and facilitates STING translocation from the ER to Golgi [94]. The inactive rhomboid protein 2 (iRhom2), an ER membrane protein containing seven transmembrane domains, recruits Translocon-associated protein (TRAP $\beta$ ) to the STING complex to facilitate its translocation [95]. iRhom2 also recruits the deubiquitinating enzyme eukaryotic translation initiation factor 3 subunit F (EIF3S5) to maintain stability of STING by removing its K48-linked poly-ubiquitin chains [95]. At the late phase of DNA viral infection, Sentrin-specific protease 2 (SEN2) desumolyates STING facilitating its degradation [96].

Other regulators of STING include autophagy-related proteins. Activated STING mediates autophagy and subsequently its own autophagic degradation through its direct interaction with the microtubule-associated light chain 3 (LC3) and p62/ Sequestosome-1 (SQSTM1) [23, 97]. Unc-51 like autophagy activating kinase (ULK1) phosphorylates activated STING to negatively regulate its function and facilitate its lysosomal degradation [29]. Toll-interaction protein (TOLLIP) was recently identified as a stabilizer of STING through direct interaction with its N-terminus to prevent its degradation and ER localization. In the same study, TOLLIP and Inositol-Requiring Enzyme 1 (IRE1 $\alpha$ ) were shown to have competing activities to maintain STING protein resting state levels [98].

Direct activation of STING by delivering CDN into cells by various means have been the subject of extensive research since the beginning of the last decade due to its effectiveness in antitumor and antiviral therapeutics. However, most of these methods have not been



successful due to the high hydrophobicity of the plasma membrane and toxicity of chemicals used to accomplish its reversible permeabilization [99]. Elucidation of the different pathways regulating STING provides novel insights into antiviral and anti-inflammatory therapeutics. Induction of STING signaling and subsequent IFN response by modulating one or more of its regulators are now being explored. At the opposite end, regulators of STING can serve as potential targets for small molecule inhibition/activation, in mitigating the effects of STING overactivation in patients with STING-dependent interferonopathies. For instance, 4-octyl-itaconate (4-OI), an activator of Nrf2, was proven to be effective in lowering STING-dependent type I IFNs release in fibroblasts from SAVI patients [62].

## **2. IFN-independent functions of STING**

### **2.1 Cellular processes regulated by STING**

Several cellular processes have been found to be regulated by STING (Figure 2). Chronic activation of STING by a gain-of-function mutation or treatment with STING agonists cause **apoptosis/cell death** of certain immune cells, including B cells [100], T cells [101, 102] and monocytes [103]. Activated STING induces apoptosis and NLR family pyrin domain containing 3 (NLRP3) activation in myeloid cells independently of its canonical role in type I IFNs signaling. Upon activation, STING translocated to lysosomes, inducing lysosomal cell death. The resulting drop in cytoplasmic K<sup>+</sup> subsequently activates NLRP3, leading to formation of inflammasome [104]. In addition to immune cells, activation of STING-IRF3 signaling also induces apoptosis of hepatocytes in patients with alcoholic liver disease (ALD). Ethanol induces ER stress and triggers the association of IRF3 with STING. Activated IRF3 then associates with the proapoptotic molecule B-cell lymphoma 2-associated X protein (Bax) and contributes to apoptosis. In this context, deficiency of STING prevents hepatocyte apoptosis [105].

Moreover, STING also activates **autophagy** through a mechanism that is both TBK1- and IFNs signaling-independent. Upon cGAMP binding, STING translocates to the ERGIC and serves as a membrane source for the lipidation of autophagy-related protein 8 (ATG8)/LC3, an essential factor for autophagosome biogenesis. LC3 lipidation is a hallmark of autophagy and leads to maturation of autophagosome. This cGAMP-induced autophagy was shown to be important for the clearance of DNA and viruses in the cytosol [25].

Additionally, STING signaling has also been shown to induce **necrosis** in a bone marrow-derived macrophage model [106]. The same study reported that a synergy between tumor necrosis factor (TNF) and IFN pathways, both of which act downstream of STING signaling, is necessary for the initiation of necrosis. This suggests a crucial role of STING activation in the induction of necrosis.

STING was also shown to promote **mitophagy** through TBK1 activation. Activation of cGAS-STING signaling leads to the phosphorylation of several mitophagy receptors including the ubiquitin- and LC3-binding domains of optineurin (OPTN) and p62/SQSTM1 by TBK1, which creates an amplification loop inducing selective autophagy of damaged mitochondria [107]. Phosphorylated TBK1-dependent autophagy adaptors has already been described in Parkinson's disease as a major step in efficient mitophagy [108].

STING also regulates **cell proliferation** by regulating the cell cycle [109]. STING deficiency in murine and human cancer cells leads to increased proliferation compared to wild-type cells. STING deficiency results in activation of cyclin-dependent kinase 1 (CDK1), facilitating onset of S and M phase of the cell cycle. STING also seems to play a critical role in proliferation of immune cells. Indeed, a recent study showed that STING activation reduces the proliferation of T lymphocytes. Interestingly, this activity was independent of TBK1-IRF3

recruitment and subsequent IFNs production but required a distinct C-terminal domain of STING that activates NF- $\kappa$ B. [101].

STING can also fine-tune IFNs response and negatively regulate IFI16 to avoid excessive IFN-I production. STING directly interacts with IFI16 and facilitates its degradation via the ubiquitin-proteasome pathway by recruiting the E3 ligase TRIM21 [110].

### 2.3 Crosstalk of STING with metabolic pathways

Several studies highlight a key role of STING as a regulator of lipid metabolism but also regulation of STING by fatty acid-derived metabolites (Figure 3). STING regulates **metabolic reprogramming** in infected macrophages. In this context, STING activation leads to increase in succinate and mitochondrial reactive oxygen species (mROS) that causes HIF-1 $\alpha$  stabilization allowing glycolytic metabolic shift [111]. How STING regulates succinate production is yet to be explored but very recent studies revealed a previously unknown role of STING in **lipid metabolism** that could be part of the answer. In *Drosophila* [51], STING was found to interact with enzymes involved in biosynthesis of long-chain fatty acids (LCFA) such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN). The deletion of STING renders *drosophila* more sensitive to starvation and oxidative stress, in parallel they present reduced lipid storage, and downregulate the expression of lipid metabolism genes. These results demonstrate previously undescribed effects of STING deficiency: reduced FASN enzyme activity and erratic ACC localization [51]. Another study revealed that, independently of its function in inflammatory responses, STING regulates metabolic homeostasis in mammalian models. Indeed, STING inhibits the Fatty acid desaturase 2 (FADS2) rate-limiting enzyme, necessary for the desaturation of dietary Omega-3 ( $\Omega$ -3) and Omega-6 ( $\Omega$ -6) polyunsaturated fatty acids (PUFAs). The PUFAs synthesized by FADS2 in turn inhibit STING, thereby regulating type I IFN responses. This cross-regulation balances metabolic and inflammatory homeostasis [35]. Moreover, another paper by Kanno et al., shows that attenuation of monounsaturated fatty acid (MUFA) production in CD4<sup>+</sup> T-cells causes activation of the cGAS-STING pathway and increases basal expression of IFNs and ISGs. Expression of genes associated with lipid metabolism was found to be reduced during infection with Influenza virus. This indicates that alteration of MUFA metabolism in T-cells during viral infection induces activation of the cGAS-STING pathway [112]. The exact mechanism of this regulation is still under investigation.

As stated previously, suppression of STING by Nrf2 is thought to be a manifestation of the role of Nrf2 in metabolic reprogramming. This reprogramming is characterized by a glycolytic shift among other things and is triggered by activation of Nrf2 upon bacterial infection or stimulation with LPS which engage TLR4 or TLR7 receptors. Unlike STING, expression of other signaling molecules of the innate immune system like TBK1, IFI16, MAVS and RIG-I do not decrease upon Nrf2 activation [62]. This highlights the role of STING in metabolism that must be mitigated for effective metabolic reprogramming.

As already discussed, accumulating evidence indicates that STING plays an important role in regulating glucose and insulin sensitivity via inflammatory responses. However, recently STING expression was shown to be essential in pancreatic  $\beta$ -cells to allow normal **insulin production**. Indeed, STING deficiency in those cells leads to a decreased expression of genes required for proper functioning of  $\beta$ -cells [113]. The impact of cGAMP administration to high fat diet (HFD)-fed mice has been tested and surprisingly cGAMP was shown to ameliorate glucose homeostasis and insulin sensitivity as well as decreasing diet-induced liver and adipose tissue inflammation [114]. These data show that cGAMP exerts cell-type-specific anti-inflammatory effects independently of STING suggesting new cGAMP target protein. Recently FADS2, a desaturase involved in lipid metabolism, was shown to interact with and to be activated by

cGAMP [35]. As FADS2 is highly expressed in liver and adipose tissue, effect of cGAMP treatment on glucose metabolism and inflammation could be in part linked to its activation.

Interestingly, the loss-of-function STING mutant HAQ was shown to be defective for CDN detection [55], but presents a higher affinity for the Fatty acid desaturase 2 (FADS2), suggesting a stronger ability to regulate PUFA desaturation [35]. The involvement of the HAQ haplotype of metabolic health in populations, whether this confers any evolutionary advantage, and the consequences in response to pro-inflammatory stimulus remains unexplored.

## 2. STING in diseases

Chronic inflammation feeds the development and progression of many chronic pathologies. Dysregulation of STING activation leads to several inflammatory pathologies, including inflammatory disorders, cancer, and metabolic disorders. Considering the role of STING in the regulation of metabolic homeostasis and the fact that concerted alterations of metabolic and inflammatory parameters are witnessed in several human pathologies, it is tempting to hypothesize that both functions of STING may be involved in determining the amplitude, breadth and symptoms associated with these diseases.

### 2.1 STING-dependent Type1 Interferonopathies

The subset of inflammatory disorders in which STING activation has been clearly identified as causative are of particular interest to this review. Type I Interferonopathies are genetic diseases where persistently enhanced IFN signaling is observed in patients [115, 116]. Some Type I Interferonopathies associated with aberrant innate immune signaling directly implicate STING protein. Aberrant and chronic activation of STING leads to exaggerated inflammatory response due to a surge in IFNs production. Three groups of Type I Interferonopathies have been shown to be dependent on STING activation.

The first type of STING-dependent interferonopathy arises due to loss-of-function mutations in cytosolic exonucleases that degrade DNA which may leak from the nucleus or mitochondria. A prime example of this type of pathology is the **Aicardi-Goutières Syndrome (AGS)**, an autosomal recessive (rarely dominant) progressive infantile familial encephalopathy characterized by severe inflammation, cerebral white matter abnormalities and intellectual disabilities. AGS patients exhibit mutations in enzymes such as the exonuclease TREX1 that prevent accumulation of cytosolic self-DNA. Similar to AGS patients, *Trex1(-/-)* mice exhibit autoimmune and inflammatory phenotypes that are associated with an elevation of ISGs. Activation of cGAS-STING pathway in this model mediates this phenotype and genetic ablation of cGAS in *Trex1(-/-)* mice eliminates all detectable pathological and molecular phenotypes [117].

The second type includes diseases which occur due to obstructions in the proper trafficking of STING. Mutation of the coatamer protein complex subunit alpha (COPA) gene, encoding the  $\alpha$ -COP subunit, causes a rare immune deregulatory disease known as COPA syndrome [118]. COPA syndrome results from dominant-negative mutations in the COPA gene, leading to sustained STING activation due to abnormal trafficking [119]. In this disease, STING cannot be recycled from the Golgi nor correctly degraded leading to sustained activation of IFN response [120, 121].

A third type of STING-dependent type I interferonopathy is caused by gain-of-function mutation in STING itself. STING-associated vasculopathy with onset in infancy (SAVI) is a prominent example of such a disease. SAVI is a rare, genetic auto-inflammatory disorder, characterized by neonatal or infantile onset systemic inflammation and small vessel vasculopathy. Patients show pulmonary and joint lesions as well as severe skin inflammation

particularly affecting the face and digits and resulting in ulceration, eschar formation, and necrosis [122]. Patients exhibit hyperactivation of STING leading to constitutive phosphorylation of STAT1 and a strong transcriptional ISG signature accompanied by increased levels of interferon-induced cytokines [122]. This pathology is a result of *de novo* [122] or inherited [123] gain-of-function mutations in the STING-encoding gene *TMEM173*. At first, three *de novo* mutations in *TMEM173*, including variants V147L, N154S, V155M were first discovered in six patients [122]. Since then, several additional SAVI patients have been identified with both the initially described SAVI STING variants [124, 125] and recently identified variants [126]. N154S and V155M, the two most frequent mutations, cause constitutive activation of STING independently of CDN binding. STING mutants translocate from the ER to the ERGIC and the Golgi and can recruit TBK1 and activate type I IFN signaling [28]. Knock-in of the murine orthologues N153S and V154M of human variants N154S and V155M respectively, were introduced into mouse models to better study and understand SAVI disease. These mice present symptoms similar to those experienced by SAVI patients including spontaneous development of skin and lung disease and premature death. Against all expectations, the pathology induced by constitutive STING activation in those mouse “SAVI” models seems to be largely independent of type I IFN induction. Indeed, skin and lung lesions persisted even when “SAVI” mice (N153S STING variant) were also deficient for the transcription factor IRF3 [127] or (V154M STING variant) the IFN- $\alpha/\beta$  receptor (*Ifnar*) [128]. The N153S and V154M SAVI mouse models present defects in immune cell populations, particularly in T, and NK cells; a feature shared with SAVI patients.

Apart from elevating interferon levels via IRF3 signaling, impact of STING activation on fatty acid metabolism can further aggravate type I interferonopathies. Severe pathological manifestations of STING-dependent interferonopathies might also be linked to PUFA imbalance due to the disturbance of metabolic homeostasis by activated STING. As already discussed, a recent study by Vila et. al., shows the inhibitory action of STING on *FADS2*; the same study also reports increase in omega-6/omega-3 ratio in case of chronic inflammation in murine model of AGS. Increase in omega-6 derivatives, particularly arachidonic acid, feeds chronic inflammation because it is the precursor of pro-inflammatory lipid mediators like cytokines and eicosanoids [129]. Additionally, recent studies have also suggested that disturbance in long chain fatty acid metabolism is the likely cause of early encephalopathy in AGS patients [130]. Although the exact mechanism is not yet understood, it might be related to improper central nervous system (CNS) myelination during development.

Even though STING activation has been shown to be responsible for chronic type I IFN signalling in these type I interferonopathies, it is important to note that the range of symptoms experienced by patients is very broad. For instance, AGS patients show in utero or post-natal disease-onset usually within the first year of life, characterized by a sub-acute encephalopathy and a loss of previously acquired skills [131]. Strikingly both SAVI and COPA syndrome have significant clinical overlap, but are distinct from AGS, with notably severe inflammatory lung disease [132]. Those discrepancies will need to be further explored in the future to better understand the divergence of symptoms and the role of STING, outside IFN signalling, in the clinical picture of type I interferonopathies.

### 2.3 Role of STING in fostering metabolic/obesity co-morbidities

Many studies have highlighted a major role of chronic low-grade inflammation in the interplay between obesity and metabolic complications and co-morbidities [133]. Obesity is associated with various metabolic diseases such as type 2 diabetes characterized by hyperglycemia, cardiovascular disease or non-alcoholic fatty liver disease (NAFLD) [134]. Adiposity-associated inflammation is a key player in obesity-induced insulin resistance and

several other complications [1, 135, 136]. As a consequence, several studies explored the role of cGAS-STING pathway in adipose tissue-induced inflammation during obesity.

Impaired mitochondrial function and promotion of cytosolic mtDNA (mitochondrial DNA) release during high fat diet feeding has been described in multiple papers as a trigger for cGAS-STING pathway and obesity-induced inflammation. High fat diet was shown to decrease adipose tissue expression of a mitochondrial chaperone-like protein called DsbA-L (Fat-specific knockout of disulfide-bond A oxidoreductase-like protein). This downregulation impairs mitochondrial function, favors mtDNA release, and promotes inflammation in adipose tissue by activating the cGAS-STING pathway [137]. Mitochondrial stress-activated cGAS-STING pathway in adipocytes was also shown to decrease cAMP levels and PKA signaling, thus reducing thermogenesis [138]. Palmitic acid (PA) treatment and diet-induced obesity causing mitochondrial damage and leakage of mtDNA were also shown to induce endothelial dysfunction. IRF3 activation induces ICAM-1 expression promoting monocyte-endothelial cell adhesion favoring inflammation [139]. Hippo–YAP pathway via mammalian Ste20-like kinases 1 (MST1), induced by activated IRF3, is inhibited in endothelial cells treated with PA causing dysregulation of angiogenesis. This mechanism could explain reduced angiogenesis and wound healing in diabetic patients [140]. Furthermore, activation of the STING pathway plays a prominent role in facilitating vascular immunity. *In vivo* studies have shown STING-mediated vascular normalization and expression of adhesion molecules in tumor endothelial cells, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin [141, 142], while overall angiogenesis was reduced. The decreased proliferation of endothelial cells, has been attributed to STING-mediated inhibition of Yes-associated protein signaling [143].

Obesity is associated with an increased risk of non-alcoholic fatty liver disease (NAFLD). There are many evidences pointing towards the involvement of the innate immune system in promoting NAFLD [144, 145]. In this context cGAS-STING pathway activation was shown to promote hepatocyte injury and dysfunction by inducing inflammation and apoptosis [146]. Chronic exposure to the STING agonist DMXAA led to hepatic steatosis and inflammation. In this study mtDNA was again involved in STING-induced inflammation in liver Kupffer cells (KFs) [147]. In line with these results, sequestration of mtDNA by mitochondrial transcription factor A (TFAM) was shown to be crucial to avoid STING activation leading to inflammation and fibrosis in kidney diseases [148]. Finally, SARS-CoV-2 virus was shown to promote aberrant inflammation via the activation of cGAS-STING signaling. This indirect activation was caused by release of mitochondrial DNA in endothelial cells [149].

The expression levels and/or activities of key players of the cGAS-STING pathway are significantly upregulated in obesity [137, 150, 151]. Several papers demonstrated a beneficial effect of TBK1 loss or inhibition in obese condition. TBK1 deletion has an overall protective effect on metabolic parameters in mice on high fat diet. This is due to the removal of the inhibitory effect of TBK1 on insulin receptors [152]. It was also shown that TBK1 deletion or inhibition by the drug Amlexanox in obese mice reduces inflammation and immune cells infiltration, increases energy expenditure, leading to weight loss, improved insulin sensitivity, and decreased liver steatosis [137]. Activated TBK1 directly inhibits 5' AMP-activated protein kinase (AMPK) to repress mitochondrial activity and increase energy storage [151]. It also suppresses the mammalian target of rapamycin complex (mTORC1), that coordinates cell metabolism and growth in response to nutrients and growth factors [153]. IRF3 was also shown as a major transcriptional regulator of adipose inflammation and is involved in maintaining systemic glucose and energy homeostasis [154].

The STING HAQ/Q293 haplotypes protect against obesity-associated risks in individuals with aging-associated diseases especially cardiovascular disease (CVD) related to chronic low-grade systemic inflammation [155]. This is because apart from inducing DNA damage [156], obesity also causes release of mitochondrial DNA, induced by the presence

free fatty acids in the cytosol [139]. These cytosolic DNA trigger the cGAS-STING pathway leading to chronic inflammation. Therefore, risk of aging-related diseases is considerably lowered by hypomorphic STING mutants which reduce the sensitivity of the cytosolic DNA sensing pathway towards CDNs in the long term.

#### 2.4 Role of STING signaling in neuro-degenerative and neuro-immunological diseases

Many studies have associated STING with degenerative changes in the brain. Its activation seems to be the cause of progressive degeneration in some cases but protective in others.

Ataxia-telangiectasia, also referred to as ataxia–telangiectasia syndrome or Louis–Bar syndrome, is a rare and autosomal recessive disease-causing severe disability including neuro-degeneration. This disease is caused by mutations in the ataxia-telangiectasia mutated (ATM) gene, which encodes a kinase in response to DNA damage (DNA double-strand breaks). Generation of an ATM-deficient rat model developing neurodegenerative phenotypes [157] showed accumulation of cytosolic DNA in Purkinje cells, microglia, and motor neurons together with increased IFN $\beta$  expression. These results suggest that activation of the cGAS-STING signaling pathway by genomic instability due to ATM deficiency leads to neuroinflammation. STING has also been implicated in Niemann-Pick disease type C, a neurovisceral disorder. The lysosomal membrane protein Niemann-Pick type C1 (NPC1) was found to be a cofactor necessary for STING trafficking, NPC1 interacts with STING and recruits it to the lysosome for degradation. Loss of NPC1 leads to less STING degradation resulting in increased inflammation [86]. Recently, cGAS-STING pathway-induced inflammation was shown to drive neuro-inflammation and sustain Parkinson's disease. Mutations in parkin, an E3 ubiquitin ligase, and PINK1, a ubiquitin kinase, cause early onset Parkinson's disease [158, 159]. Due to the loss of Parkin- and PINK1-mediated protection against mitochondrial stress, mtDNA leakage into the cytosol induces cGAS-STING pathway activation and subsequent cytokines production drives neuro-degeneration in the substantia nigra pars compacta of the midbrain [160].

Administration of cGAMP to activate STING, significantly ameliorates cognitive deficits, improves pathological changes, decreases Amyloid- $\beta$  plaque load, and reduces neuron apoptosis in the Alzheimer's disease mice model (APP/PS1 transgenic). The stimulation of cGAMP-STING-IRF3 pathway induces upregulation of triggering receptor expressed on myeloid cells 2 (TREM2). TREM2 regulates microglia polarization from M1 towards M2 phenotype leading to a reduction of neuro-inflammation in Alzheimer's disease [161]. Multiple sclerosis is a chronic autoimmune disease that affects the central nervous system, especially the brain, spinal cord, and optic nerves. It is characterized by the demyelination and subsequent neurodegeneration of axons. Being an immune-mediated disease, it responds to immunomodulatory therapies. STING activation and type I IFNs production play a therapeutic role in multiple sclerosis reducing neuroinflammation and microglial reactivity [162]. STING was shown to be involved in nociception in sensory neurons. STING activation promotes robust antinociception by induction of type-I interferons, which promptly suppress the excitability of nociceptors [163]. Thus, treatment with STING agonists shows great analgesic potential in combating pain during advanced stages of cancer [164].

#### 2.5 STING in other inflammation-related pathologies

Apart from the several categories of diseases discussed till now, both interferon-dependent and -independent functions of STING play important roles in other inflammation-related pathologies.

Systemic lupus erythematosus is a chronic autoimmune disease characterized by the production of autoantibodies specific for nuclear antigens. The exact cause of this disease remains unclear, however type I interferons play important roles in its pathogenesis and

progression [165]. The role of STING in lupus is controversial as on one hand, mutations leading to STING activation has been linked to a familiar form of lupus erythematosus [123] while on the other hand, STING potently suppressed inflammation in a murine model of systemic lupus erythematosus [166]. However, recent results suggest that targeting STING to decrease IFNs production in lupus patients could be a therapeutic option [167, 168]. Rheumatoid arthritis is a chronic systemic autoimmune disease hallmarked by infiltration and destruction of cartilage and bone by immune cells. Several studies have pointed out a role of IFNs in its pathogenesis [169] and cGAS-STING activation was shown to promote inflammation in rheumatoid arthritis patients [170].

Myocardial infarction results in release of nucleic acids which activates cGAS-STING pathway leading to induction of IFN genes. Inhibition of cGAS-STING pathway increases the abundance of reparative macrophages which results in enhanced repair and improved hemodynamic performance [171, 172]. Recently, STING was shown to be contributing to cardiac hypertrophy due to pressure overload in response to ER stress [173]. STING signaling pathway has also been linked to age-related macular degeneration. In this context, macular degeneration characterized by retinal pigmented epithelium (RPE) death is driven by a non-canonical inflammasome pathway that activates caspase-1 and caspase-4, and requires production of cGAS-STING-dependent IFN- $\beta$  [174].

STING activation in the digestive pathologies has also been reported. STING is involved in the host's response to acutely-induced colitis as STING activation repolarize M2 macrophages into M1-like subtype that is pro-inflammatory in nature and leads to aggravation of symptoms [175]. Another study suggests that induction of the anti-inflammatory cytokine IL-10 by STING balances the effects of pro-inflammatory cytokines, facilitating homeostasis during enterocolitis [176]. Chronic pancreatitis is an inflammatory disease with progressive fibrosis leading to exocrine and endocrine dysfunction. STING signaling is important in regulating adaptive immune responses by reducing the generation of IL-17A in chronic pancreatitis and thus presents a novel therapeutic target for this disease [177]. Unlike the chronic condition, acute pancreatitis is further aggravated by STING activation manifested by severe inflammation and acinar cell death [178].

A proper understanding of the full array of interactions between STING and one or more mediators of these pathologies will go a long way in investigating more possible interferon- and CDN-independent roles of STING underlying their pathogenesis.

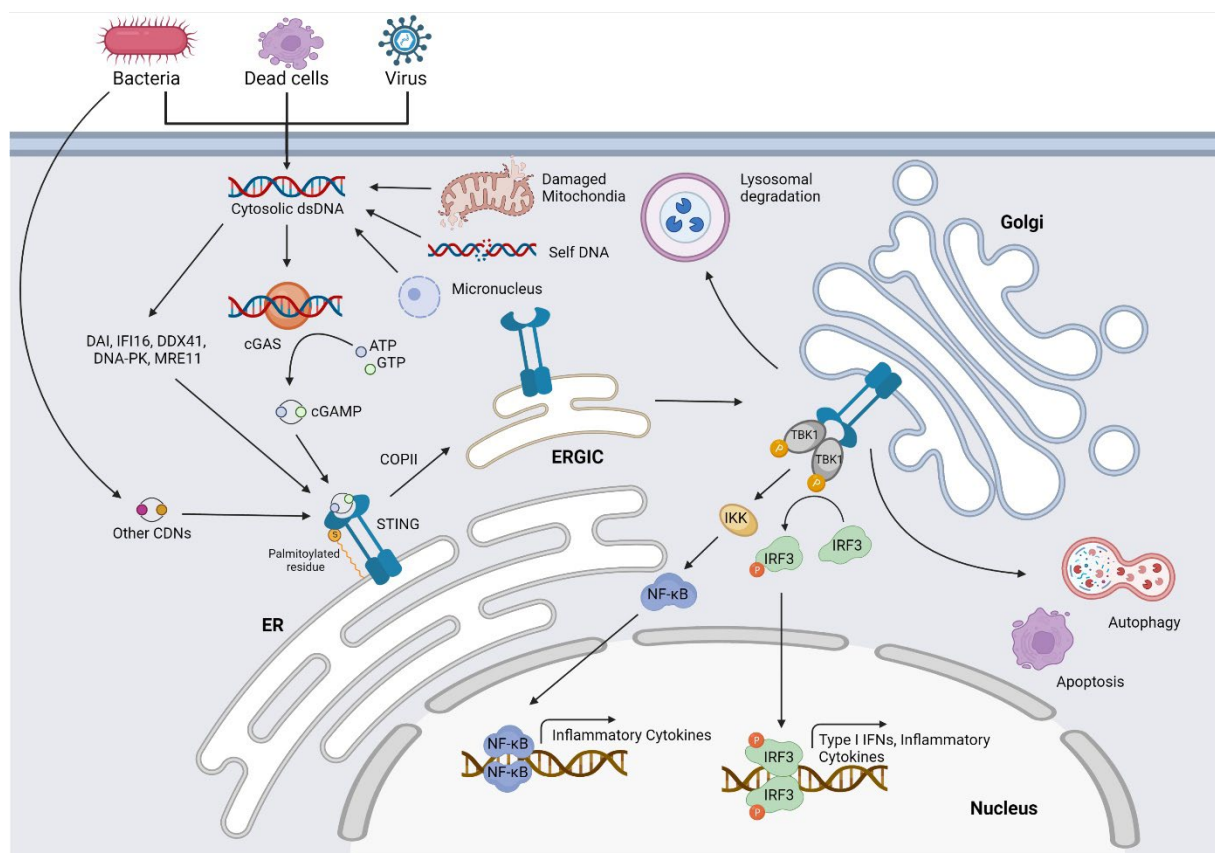
### **Conclusion:**

Although significant progress has been made in elucidating the role of the cGAS–STING signaling pathway as a host defense mechanism, recent findings demonstrate that this pathway has functions beyond cytosolic DNA sensing, in particular in metabolic contexts. Evolutionary analysis also suggests that the role of STING in integrating and modulating metabolic cues is ancient, largely conserved, and possibly the primordial function of STING. Interestingly, metabolic pathways that crosstalk with STING, such as unsaturated fatty acids (MUFAs and PUFAs) metabolism, are also involved in the control of STING-independent inflammatory responses. Indeed, while PUFAs can directly inhibit STING [35]), they can also be processed into lipid mediators (oxylipins) that bear immunomodulating properties. Thus, one can hypothesize that STING alleles that are expressed in organisms devoid of an IFN signaling pathway may control inflammatory responses through regulating the generation of immune-modulatory metabolites.

Importantly, chronic STING activation is a central driver of tumor immunogenicity. Recent reports indicate that STING activity in early tumors can prevent tumor initiation [179] while at later stages, chronic STING activation is essential for tumor cell survival [180] and is a poor prognostic marker for cancer patients [179, 181]. To fully appreciate the role of STING

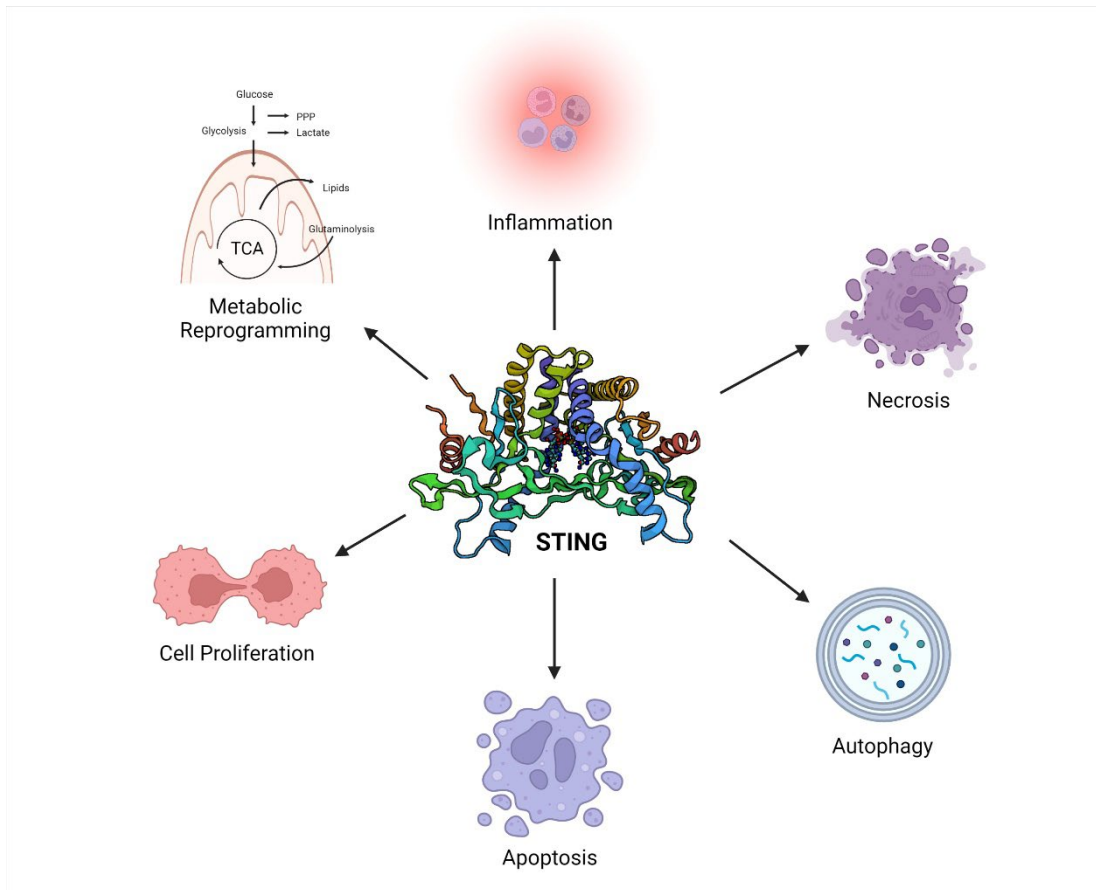
in tumorigenesis, investigation of the crosstalk between STING expression and inflammatory activity and metabolic rewiring is essential. Indeed, tumor cell-intrinsic metabolic rewiring is essential to tumorigenesis [182]. In addition, communication between immune cells and their neighboring cells in a tissue microenvironment is vital for the adaptation to dynamic nutritional and environmental statuses. These parameters are also key points to address in STING-targeting therapeutic avenues. Indeed, STING activation in the tumor microenvironment is likely to foster metabolic shifts that may feed tumorigenesis, fostering adverse effects. Therefore, the impact of STING activation/targeting on both inflammatory responses and metabolic parameters is important to investigate in order to fully unravel the potential of these approaches.

## Figures and Legends:

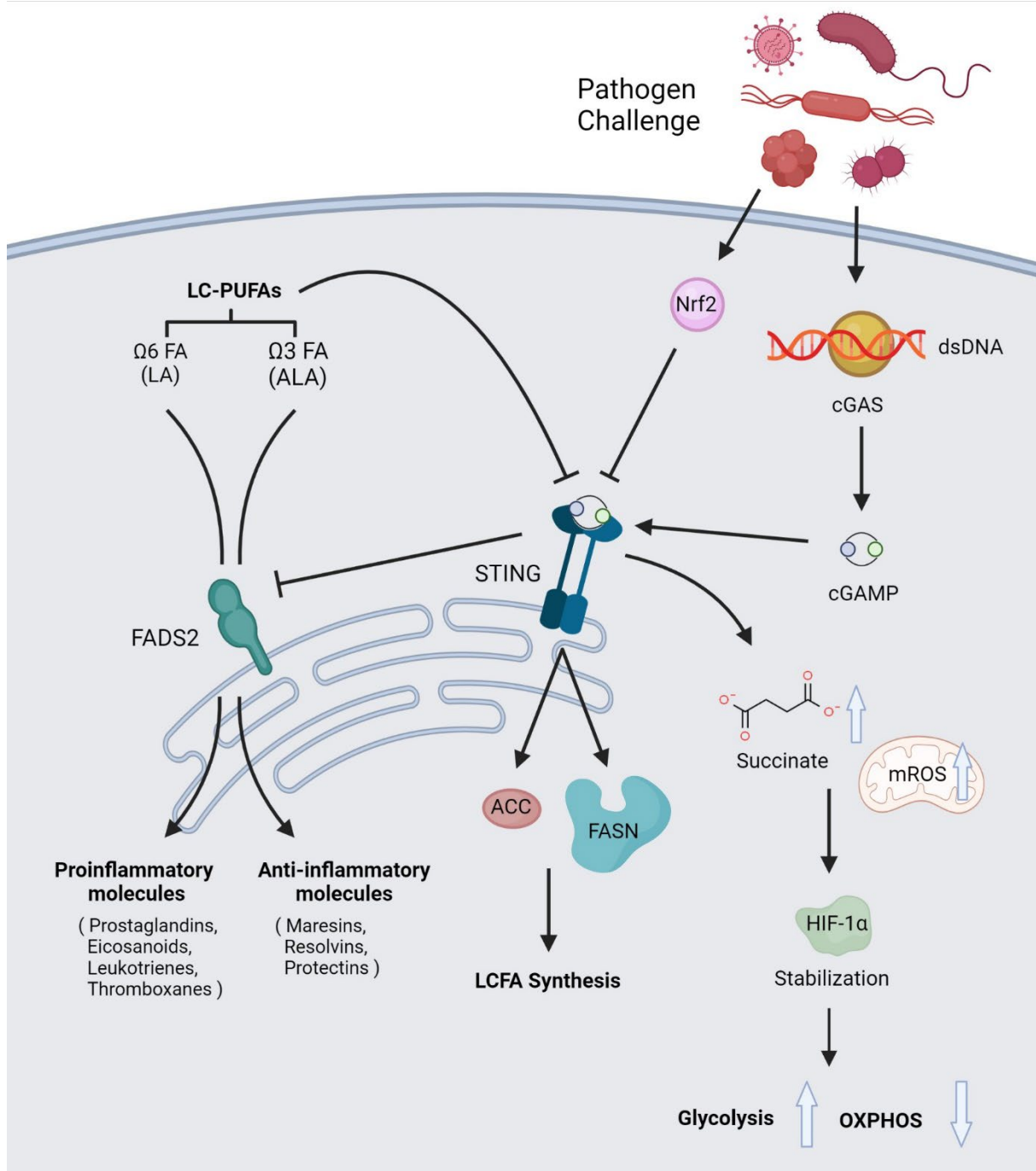


**Figure 1: Overview of the cGAS-STING pathway of cytosolic DNA sensing.** The presence of dsDNA in the cytosol can result from pathogen infection, dead cells or leakage from nucleus (DNA damage) or mitochondria. cGAS binds to, and is enzymatically activated by cytosolic dsDNA, leading to synthesis of 2'3'-cGAMP from ATP and GTP. cGAMP binds to ER-resident STING, which undergoes conformational changes leading to oligomerization, liberation from anchoring factors (such as STIM1, not depicted in figure), interaction with trafficking factors (for example, SEC24/23, STEEP, not depicted in figure) and eventually translocates to the ERGIC through COPII vesicles and then to the Golgi apparatus. In the Golgi, STING binds to and activates TBK1 (by autophosphorylation) and IKK. TBK1 then phosphorylates IRF3 which undergoes dimerization and translocates to the nucleus to induce transcription of type I IFNs and several inflammatory chemokines. IKK activates the transcription factor NF-κB which also induces transcription of inflammatory cytokines. IRF3 and NF-κB acts in synergy to induce high levels of type I IFN and proinflammatory cytokines. Activated STING also initiates the process of autophagy and apoptosis which helps in clearing pathogens and cytosolic DNA. Lastly, STING from both Golgi and autophagosomes is degraded in the lysosome.





**Figure 2: STING is central to many processes deciding the fate of the cell.** Activation of STING can trigger inflammation, apoptosis, autophagy, necrosis, cell proliferation and metabolic reprogramming.



**Figure 3: Schematic depiction of the crosstalk between STING and Metabolism.** (1) Activation of STING by 2'3'-cGAMP in response to cytosolic dsDNA leads to increase in concentration of succinate and mROS which stabilizes HIF-1 $\alpha$ . HIF-1 $\alpha$  facilitates transcription of genes that promote metabolic adaptation to hypoxia, inducing a glycolytic shift in the cell. (2) Microbial infection activates the metabolic regulator Nrf2 which directly inhibits STING. This role of Nrf2 is thought to play a part in metabolic reprogramming of the infected cell. (3) FADS2 is involved in the synthesis of highly unsaturated fatty acids from LC-PUFA precursors. Immunomodulatory molecules derived from  $\Omega$ 3 PUFAs have anti-inflammatory properties while those derived from  $\Omega$ 6 PUFAs have pro-inflammatory properties. STING directly inhibits FADS2 and is in turn inhibited by LC-PUFAs in the cytosol.

**Table:**

Table I: Direct Protein Regulators of STING

| Regulator   | Type of Regulation | Reference |
|---|--------------------|-----------|
| TANK Binding Kinase (TBK1)  | Positive           | [31]      |
| STING1 ER Exit Protein (STEEP)  | Positive           | [77]      |
| TIR Domain Containing Adapter Protein (TRIP)                                | Positive           | [78]      |
| S6 Kinase (S6K1)  | Positive           | [79]      |
| Zinc Finger DHHC-Type Containing 1/11 (ZDHHC1/11)                           | Positive           | [81] [80] |
| NLR Family CARD Domain-Containing Protein 3 (NLRC3)                         | Negative           | [83]      |
| NLR Family Member X1 (NLRX1)  | Negative           | [82]      |
| Protein Phosphatase Mg <sup>2+</sup> /Mn <sup>2+</sup> Dependent 1A (PPM1A) | Negative           | [17]      |
| Interferon-stimulated Gene 56 (ISG56)                                       | Negative           | [84]      |
| Stromal Interaction Molecule 1 (STIM1)                                      | Negative           | [85]      |
| Niemann-Pick type C1 (NPC1)   | Negative           | [86]      |
| Nuclear factor erythroid 2-related factor 2 (Nrf2)                          | Negative           | [62]      |
| Tripartite Motif Containing Protein 32 (TRIM32)                             | Positive           | [88]      |
| TRIM38  | Positive           | [92]      |
| TRIM29  | Negative           | [90]      |
| TRIM30 $\alpha$   | Negative           | [89]      |
| TRIM56  | Positive           | [87]      |
| Ring Finger Protein 26 (RNF26)  | Positive           | [93]      |
| RNF5  | Negative           | [91]      |
| Autocrine Motility Factor Receptor (AMRF)                                   | Positive           | [94]      |
| inactive Rhomboid Protein 2 (iRhom2)  | Positive           | [95]      |
| Translocon-associated Protein (TRAP $\beta$ )                               | Positive           | [95]      |
| Eukaryotic Translation Initiation Factor 3 Subunit F (EIF3S5)               | Positive           | [95]      |
| Sentrin-specific Protease 2 (SEN2)  | Negative           | [96]      |
| Unc-51 like Autophagy Activating Kinase (ULK1)                              | Negative           | [29]      |
| Toll-interaction protein (TOLLIP)   | Positive           | [98]      |
| Inositol-Requiring Enzyme 1 (IRE1 $\alpha$ )                                | Negative           | [98]      |

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