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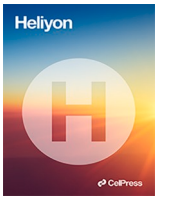

Review article

The role of the cGAS-STING pathway in metabolic diseases

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ABSTRACT

The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway is a critical innate immune pathway primarily due to its vital DNA sensing mechanism in pathogen defence. Recent research advances have shown that excessive activation or damage to the cGAS-STING pathway can exacerbate chronic inflammatory responses, playing a significant role in metabolic dysfunction and aging, leading to the development of related diseases such as obesity, osteoporosis, and neurodegenerative diseases. This article reviews the structure and biological functions of the cGAS-STING signaling pathway and discusses in detail how this pathway regulates the occurrence and development of metabolic and age-related diseases. Additionally, this article introduces potential small molecule drugs targeting cGAS and STING, aiming to provide new research perspectives for studying the pathogenesis and treatment of metabolic-related diseases.

1. Introduction

To sustain their usual physiological operations, organisms transform nutrients from the environment into energy through the metabolic. If metabolic disorders occur, cells may not be able to perform their duties, leading to chronic diseases such as metabolic-associated fatty liver disease (MAFLD), obesity, insulin resistance (IR), cardiovascular diseases, osteoporosis, and cellular aging. It is well known that genetics, environmental factors, and unhealthy lifestyles are significant contributors to metabolic disorders [1–3]. Accumulated evidence now indicates that a hallmark of metabolic disorders is chronic sterile inflammation. Danger signals produced by metabolic overload are perceived by host pattern recognition receptors (PRRs), triggering pro-inflammatory pathways and promoting mild, sustained chronic inflammation [4,5]. Thus, the close connection between immunity and metabolism is increasingly recognized.

Significant progress has been made in the study of the cGAS-STING pathway as a molecular mechanism of the innate immune system's first line of defense against pathogen infection. cGAS, as a DNA sensor protein, can recognize exogenous DNA such as nuclear or mitochondrial DNA (mtDNA) and cellular components exposed due to self-damage, activating downstream STING, promoting the expression and release of inflammatory genes [6,7]. Previous research results suggest that improper activation or inhibition of the cGAS-STING pathway is associated with metabolic diseases such as obesity [8–10], nonalcoholic fatty liver disease (NAFLD) [11,12], and osteoporosis [13]. In this context, we summarized some literature reports on the impact of the cGAS-STING pathway on metabolic

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disruption. Utilizing the cGAS-STING pathway and its related signaling molecules as potential targets for developing treatments for metabolic diseases is very promising. Therefore, we also discuss the latest advancements in novel antagonists and agonists targeting cGAS and STING. Moreover, this research lays the groundwork for future studies to deeply understand the specific roles and mechanisms of this pathway in metabolic disorders.

2. cGAS-STING pathway

2.1. Structure and localisation of the cGAS molecule

In 2013, a research team led by Zhijian "James" Chen at the University of Texas Southwestern Medical Center utilized biochemical fractionation and mass spectrometry analysis techniques to discover a novel cytoplasmic DNA sensor, cGAS, capable of recognizing double-stranded DNA (dsDNA) [6]. cGAS is part of the nucleotidyltransferase (NTase) family and is encoded by the MB21D1 gene. The cGAS species originated in humans and its structure consists of a single NTase domain and two major DNA-binding domains, this structure is composed of a flexible N-terminal domain (amino acids 1–160) and a structured C-terminal region of the NTase and Mab21 domains (amino acids 161–522) [6]. The C-terminal catalytic domain of cGAS contains a zinc finger motif, which is a crucial site for recognition of cytoplasmic DNA. Inhibiting this structure prevents cGAS from recognizing DNA. Both full-length cGAS and its catalytic domain can catalyse the synthesis of cGAMP in response to stimulation by dsDNA [14]. In the absence of dsDNA, cGAS is monomeric and has no catalytic activity. Upon binding to dsDNA, a conformational alteration in the catalytic centre of cGAS is induced, thus promoting the crosslinking of two cGAS molecules into a 2:2 dimer or higher-order complex, thereby activating cGAS. This active cGAS-DNA complex limits the structural flexibility of cGAS and stabilises the enzyme's enzymatically active conformation [15]. Xin Li and colleagues discovered that dsDNA with a length of 12 base pairs (bp) cannot effectively activate cGAS. However, dsDNA oligonucleotides with a length of 20 bp, equivalent to that of salmon sperm DNA, exhibit activity. When the length exceeds 45 bp, it can induce even stronger enzymatic activity [14]. Additionally, at low DNA concentrations, cGAS can only bind to longer dsDNA sequences. dsDNA shorter than 20 bp can induce cGAS catalytic activity in vitro only when the cGAS concentration is very high [16]. It seems that the size and concentration of dsDNA, not its sequence specificity, are the deciding factors of cGAS catalytic activity. Interestingly, the length of dsDNA that binds and activates cGAS also varies among different species [15].

Currently, there are differing perspectives regarding the localisation of cGAS in the nucleus, cytoplasm, and plasma membrane. In the initial model, the research team of Zhijian "James" Chen [6] prepared cytoplasmic and nuclear extracts of THP-1 cells. Immunoblotting and confocal immunofluorescence microscopy revealed detectable levels of cGAS in the cytoplasmic fraction, suggesting that cGAS was distributed within the cytoplasm. However, more recent studies have suggested a more complex localisation of cGAS. It is found not only in the cytoplasm but also has diverse cellular distributions, including in the cell membrane and nucleus. Barnett et al. [17] used differential ultracentrifugation to analyse the distribution of cGAS in subcellular fractions of THP-1 monocytes. They found that a substantial amount of endogenous cGAS was associated with membrane components. This led them to propose that cGAS is not solely a cytoplasmic protein but is localised to the plasma membrane through the action of its N-terminal phosphoinositide domain. It is considered a peripheral membrane protein primarily present on the plasma membranes of human and murine macrophages. Gentili et al. [18] tracked the localisation of cGAS throughout the cell cycle in stable GFP-cGAS-expressing HeLa cells. They also transfected defective cGAS into cycling 293FT cells, which led to a mixture of cells with varying localisations: primarily cytoplasmic, primarily nuclear, or mixed. The localisation of the N-terminal domain of cGAS may have been the cause of its varied activities, potentially reducing the risk of self-inflammation and autoimmunity. To determine the resting localisation of endogenous cGAS before activation, Volkman et al. [19] employed confocal microscopy and biochemical fractionation. They found that in all cells tested, the majority of endogenous cGAS was localised within the nucleus prior to its activation, regardless of whether the cells were in a rapidly dividing or postmitotic state. Therefore, to gain a deeper understanding of the cellular distribution of cGAS, studies using quantitative cell localisation are necessary.

2.2. The structure and localisation of STING

An evolutionarily conserved endoplasmic reticulum transmembrane protein, STING (also known as MITA, ERIS, MPYS, or TMEM173), is encoded by the TMEM173 gene and is composed of 379 amino acids [20]. Primarily located on the endoplasmic reticulum membrane, it is partially localised to the Golgi apparatus and mitochondrial membranes. It possesses multiple functional domains. Human STING (h-STING) is composed of a cytoplasmic C-terminal domain (CTD) and an N-terminal transmembrane domain (TM), which form a complete domain-swapped dimer [21]. The N-terminal domain is located outside the membrane and consists of four transmembrane domains that anchor STING to the endoplasmic reticulum membrane or other membrane structures. The cytoplasmic C-terminus of STING comprises 250 amino acids, forming a globular C-terminal domain that is crucial for its function. It mainly consists of a ligand-binding domain (LBD) and a C-terminal tail (CTT) [21,22]. The CTT of STING is responsible for recruiting interferon regulatory factors (IRFs) and TANK-binding kinase 1 (TBK1), leading to the activation of interferon regulatory factor 3 (IRF3) [23].

2.3. Signal transduction and regulation of the cGAS-STING pathway

Under physiological circumstances, cGAS is inactive. In the face of pathogenic invasion or cellular harm, micronuclei can be formed due to DNA damage and chromosome misalignment, which leads to the assembly of nuclear envelopes that are vulnerable to rupturing

and cGAS enrichment. cGAS is recruited and colocalises with DNA damage markers such as phosphorylated histones [6,24,25]. Upon activation, it adopts a Y-shaped structure and can form internal double helices and external extensions [26].

In 2013, Chen Zhijian and Andrea Ablasser, together with their research team, described cGAMP, the first cyclic dinucleotide to be discovered in multicellular organisms, thus elucidating the DNA-cGAS-cGAMP-STING signalling axis [6,27]. The synthesis of cGAMP involves two distinct chemical reactions occurring at the same catalytic site. Initially, cGAS catalyzes the formation of a 2′-5′ bond, followed by cyclisation to form a 3′-5′ bond, resulting in an isomer known as "2′3′-cGAMP" [28]. The synthesised cGAMP needs to be transported from the cytoplasm, where cGAS is located, to the endoplasmic reticulum membrane, where the STING protein functions as a secondary messenger [29]. However, as an anionic hydrophilic molecule, cGAMP does not readily traverse the lipid bilayer. Therefore, the group investigated how cGAMP achieves transmembrane transport. Andrea Ablasser and colleagues discovered that cGAMP is transferred from secreting cells to neighbouring cells through intercellular gap junctions [30]. Additionally, research has shown that anionic channel proteins on the cell membrane, such as SLC19A1 [31] and LRRC8 [32], can serve as transmembrane transport systems for cGAMP. Recently, Xubiao Wei and his team identified a human host defence peptide, LL-37, to be a transporter for cGAMP. With the assistance of the free peptide LL-37, cGAMP can be efficiently delivered to target cells, leading to strong activation of the STING pathway [33].

In the body, STING exists in a stable homodimeric form on the endoplasmic reticulum, maintaining a self-restrained inactive state. During pathogenic invasion or cellular damage, cGAS can recognize aberrant DNA and become activated, catalysing the production of cGAMP, which serves as a secondary signalling molecule [14,21]. The binding of STING to cGAMP leads to a conformational transformation, disrupting the connection between STING and STIM1 and augmenting the connection between STING and SEC24C, a COPII vesicle coat complex component. This triggers the relocation of STING from the endoplasmic reticulum to the ER-Golgi intermediate compartment, a critical regulatory system for STING. Additionally, binding to cGAMP triggers the release of the C-terminal tail CTT of STING and the aggregation of STING dimers [23]. This translocation process also causes the palmitoylation of cysteine residues at amino acids 88 and 91 of the N-terminal domain of STING in the Golgi apparatus, thus allowing TBK1 to be activated. TBK1 phosphorylates STING on serine and threonine residues, and phosphorylated STING exhibits increased affinity for IRFs, thereby recruiting IRF3 for TBK1-dependent phosphorylation and activation [34]. Activated IRF3 dimers translocate to the cell nucleus, where they

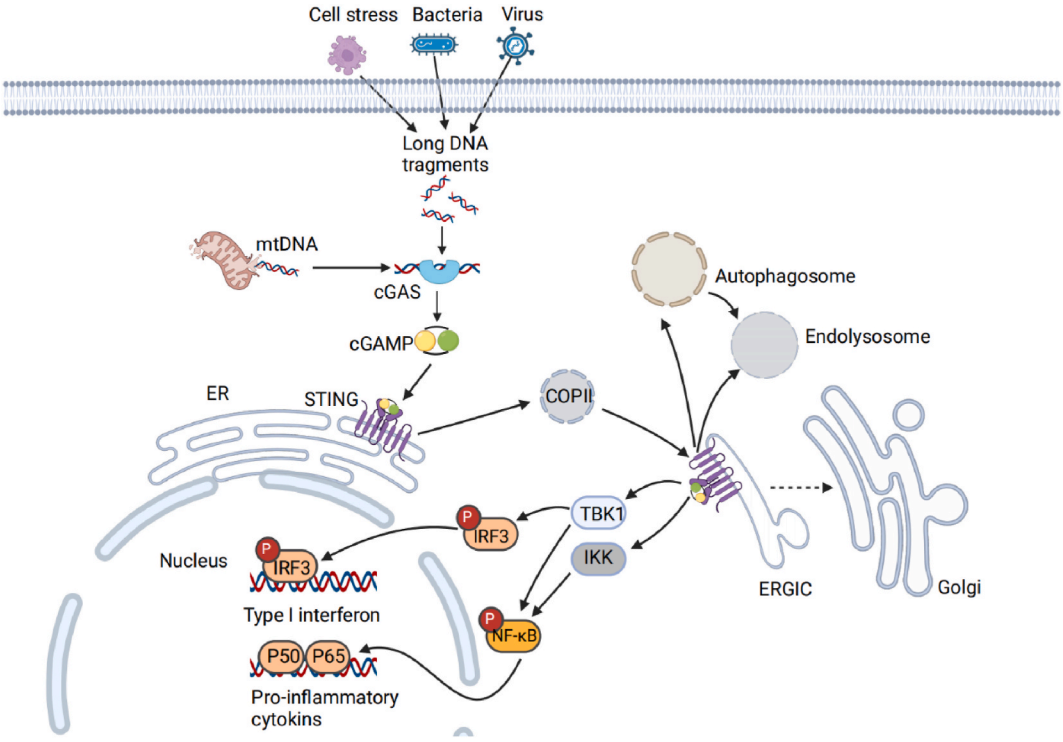

Fig. 1. The cGAS-STING Signaling Pathway. When there is invasion by pathogens (including bacteria, viruses) or cellular damage (including injured cells, mtDNA), DNA fragments accumulate in the cytoplasm. The cyclic GMP-AMP synthase (cGAS) recognizes cytoplasmic long DNA fragments and catalyzes the synthesis of 2′3′-cyclic GMP-AMP (cGAMP). cGAMP binds to the dimeric form of Stimulator of Interferon Genes (STING) located on the endoplasmic reticulum (ER) membrane, triggering the oligomerization of STING. This leads to the incorporation of STING into the Coat Protein Complex II (COPII) vesicles, initiating the translocation of STING from the ER to the ER-Golgi intermediate compartment and Golgi apparatus. STING activates TBK1, which in turn phosphorylates IRF3. Phosphorylated IRF3 then activates the expression of type I interferons (IFNs) in the cell nucleus. Activation of STING also leads to the activation of NF-κB and the formation of autophagosomes through non-classical mechanisms. NF-κB activation promotes the expression of pro-inflammatory cytokines, and eventually, STING undergoes degradation in autophagosomes and lysosomes. Created with BioRender.com.

induce the expression of type I interferons (IFNs) and various immune regulatory factors [35,36]. In addition to phosphorylation, multiple studies have suggested that the ubiquitination of STING also participates in regulating downstream activity. TRIM56, a ubiquitin ligase, binds to STING, thereby causing its ubiquitination. This promotes STING dimerisation and interaction with TBK1, thereby activating downstream pathways and subsequently inducing the production and secretion of IFNs and various inflammatory factors [37]. Additionally, the activation of STING can also lead to the activation of NF-κB through non-classical mechanisms, promoting the expression of pro-inflammatory cytokines [37]. However, excessive cGAS-STING pathway activity can amplify the inflammatory response. Therefore, this pathway is regulated by various negative feedback mechanisms, which might be related to cellular autophagy. Dong Liu and colleagues reported that STING possesses typical LC3-interacting regions (LIRs) and mediates autophagy and STING degradation through direct interaction with LC3 [38]. Upon ULK1 activation, STING is phosphorylated and targeted for autophagic degradation, subsequently limiting downstream type I interferon responses [39] (Fig. 1).

2.4. The cGAS-STING pathway participates in the pathophysiological processes of metabolism

Mitochondria are the centers of energy metabolism in the body, participating in numerous cellular signaling, cellular matrix metabolism, and apoptosis processes [40]. The development of many metabolism-related diseases, such as cellular aging and obesity, is closely related to mitochondrial dysfunction [41,42]. Juli Bai and colleagues found that mitochondrial stress-induced release of mtDNA into the cytoplasm can activate the cGAS-STING pathway, leading to an increase in chronic sterile inflammation in adipose tissue [43]. In stark contrast to nuclear genomic DNA, mtDNA lacks protective histones, making it highly susceptible to damage and disruption of its integrity. Normally, mtDNA resides within the mitochondrial matrix. However, during cellular stress or mitochondrial damage, mtDNA can be released into the cytoplasm or circulation. This release of mtDNA leads to its interaction with the DNA sensor cGAS, subsequently activating the STING-IRF3 pathway and enhancing the type I interferon (IFN) response [44–46]. So, how is mtDNA translocated from within the mitochondrial membrane to the cytoplasm? Current research, both domestic and international, offers different views. Studies have found that mitochondrial outer membrane permeabilization (MOMP) may lead to the release of mtDNA [47]. McArthur Kate and colleagues used live-cell lattice light-sheet microscopy to observe the mitochondrial network in mouse embryonic fibroblasts. They found that the activation and oligomerization of BAX and BAK proteins led to the formation of larger BAK/BAX pores in the mitochondrial outer membrane, facilitating the entry of mitochondrial matrix contents, including mtDNA, into the cytoplasm [48]. Additionally, mtDNA may also be released into the cytoplasm through the mitochondrial permeability transition pore (mPTP) or the voltage-dependent anion channel (VDAC) pore in the mitochondrial outer membrane [49,50]. Overall, these studies indicate that mtDNA stress-mediated cGAS-STING signal transduction may contribute to the progression of various metabolic disorders (Fig. 2).

3. cGAS-STING is involved in the pathophysiological processes of metabolic disorders and aging

As our foundational knowledge of the cGAS-STING pathway continues to expand, many researchers have focused in recent years on exploring its specific role in the progression of metabolic diseases. The following section examines examples of cGAS–STING pathway overactivation that leads to an overabundance of inflammation in metabolic diseases (Fig. 3).

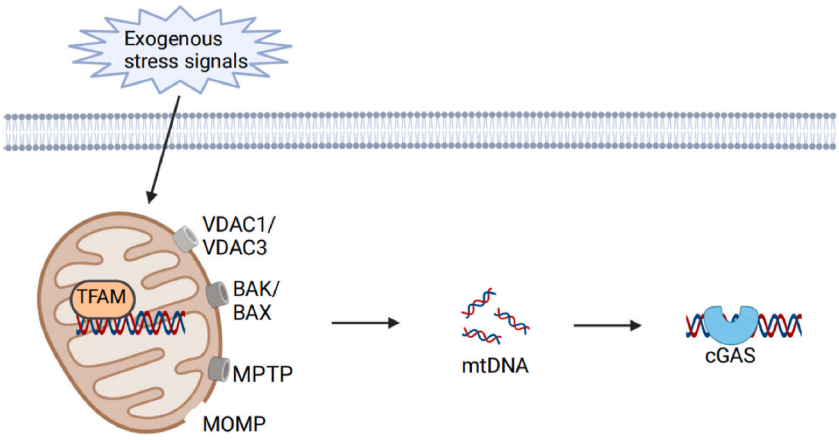

Fig. 2. The mechanism of mitochondrial DNA activation of cGAS. Within the mitochondria, transcription factor A mitochondrial (TFAM) plays a crucial role in maintaining the stability of mitochondrial DNA (mtDNA). The absence of TFAM can result in mitochondrial genomic instability and mitochondrial stress, leading to the escape of mtDNA into the cytoplasm. Additionally, exogenous stress signals may also lead to mitochondrial dysfunction. Mitochondrial DNA can be released through both mitochondrial inner membrane herniation, followed by release through BAX/BAK pores, and through the voltage-dependent anion channel (VDAC) pores in the mitochondrial outer membrane. Mitochondrial outer membrane permeabilization (MOMP) could also lead to the release of mitochondrial DNA. Furthermore, the mitochondrial permeability transition pore (MPTP) may serve as another pathway for translocating across the mitochondrial inner membrane. Created with BioRender.com.

3.1. The cGAS-STING pathway in obesity

Obesity is a chronic metabolic disorder by a plethora of pathological and physiological traits, such as excessive fat content, persistent inflammation, and insulin resistance. This condition is linked to a variety of metabolic illnesses, such as type 2 diabetes, NAFLD, cardiovascular diseases, and a variety of cancers. Studies have indicated that chronic inflammation of physiologically sterile adipose tissue is a major contributor to the emergence of obesity-induced insulin resistance and metabolic disorders [51,52]. Nevertheless, the exact mechanisms by which obesity triggers inflammation remain largely unknown. The accumulation of adipose tissue in an overweight state combined with an inflammatory reaction can lead to an increase in oxidative stress, which leads to mitochondrial membrane and DNA damage, causing mitochondrial harm. This can then cause mtDNA to be released into the cytoplasm, subsequently activating the cGAS-STING pathway and intensifying the chronic sterile inflammatory response [53]. Obesity is associated with the release of mtDNA into the cytoplasm, which is induced by FFAs. In mice fed a high-fat diet, the overall loss of expression of downstream targets of cGAS-STING, such as TBK1 or IRF3, is associated with improvements in insulin sensitivity and reduced inflammation in adipose tissue [54].

Studies have found that in high-fat diet-fed mice, the expression of TBK1 increased in adipocytes [55]. Elif et al. conducted a study on 42 patients with type 2 diabetes and NAFLD and reported that a subgroup treated with the TBK1 inhibitor amlexanox exhibited improvements in insulin sensitivity and hepatic steatosis [56]. In conclusion, the above studies indicate that the cGAS-STING pathway is closely related to obesity-induced aseptic inflammation, insulin resistance, and other metabolic disorders. However, the specific mechanisms of its action remain to be determined.

3.2. The cGAS-STING pathway in NAFLD

The prevalence of NAFLD, is increasing, and hepatic steatosis is its defining characteristic. This chronic liver disease is now the most widespread liver disease. Inflammation and fibrosis are typical symptoms of nonalcoholic steatohepatitis (NASH), yet their role in liver cell injury is still uncertain. The cGAS-STING pathway has been highlighted as a key factor in the progression of NASH, which can result in liver fibrosis, cirrhosis, and eventually liver failure [57]. The cGAS-STING pathway is activated by the release of mtDNA after liver cell injury, resulting in the expression of various inflammatory cytokines and chemokines [11]. Moreover, STING knockout alleviated HFD-induced insulin resistance and weight gain while also reducing serum cholesterol, triglyceride, and LDL levels. A previous study revealed that chronic exposure to 5,6-dimethylxanthenone-4-acetic acid (a STING agonist) induced hepatic steatosis

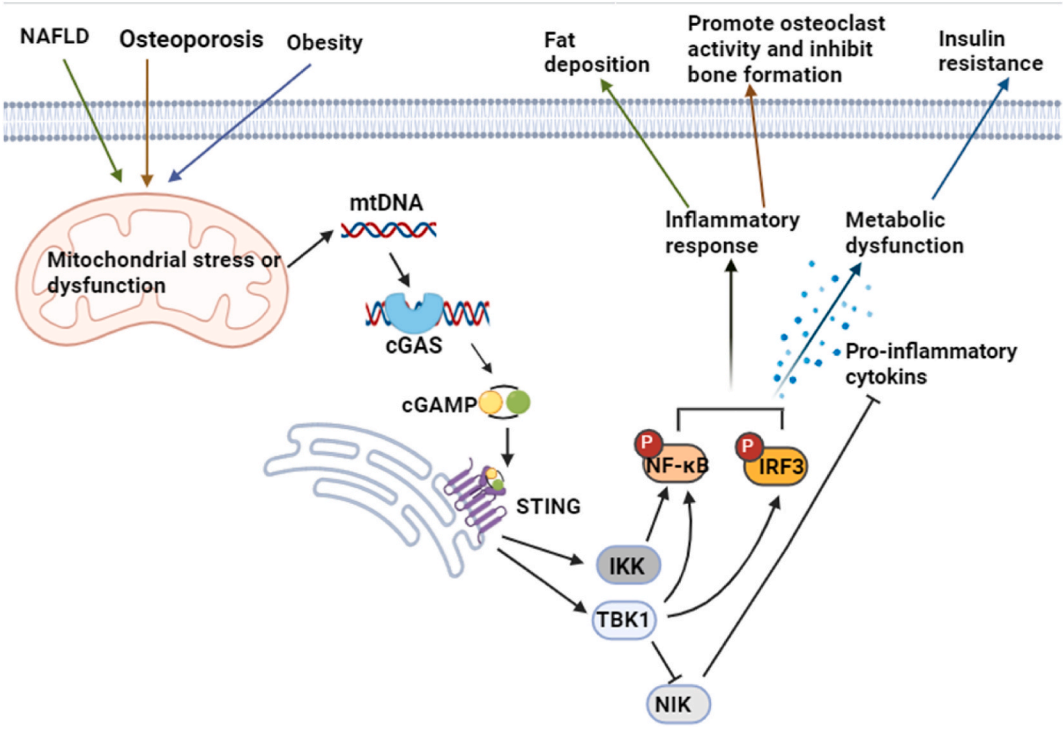

Fig. 3. The cGAS-STING pathway mediates the pathophysiological process of metabolic diseases. In diseases such as NAFLD, osteoporosis, and obesity, cGAS senses mtDNA and subsequently activates the cGAS-STING pathway. This activation leads to the activation of TBK1 and phosphorylation of IRF3, inducing the transcriptional expression of pro-inflammatory cytokines, thereby triggering corresponding metabolic dysfunctions, including lipid deposition, promotion of osteoclast activity, inhibition of bone formation, or insulin resistance. Additionally, TBK1 inhibits inflammation by phosphorylating and inducing the degradation of NF-κB inducing kinase (NIK), thereby attenuating the inflammatory response.

and inflammation in mice but not in STING-deficient mice [12]. Qiao et al. reported that mice fed a high-fat diet had increased liver expression of STING and IRF3. Knockout of either STING or IRF3 significantly reduced liver inflammation and cell apoptosis, indicating that the STING-IRF3 pathway promotes liver cell injury and dysfunction by inducing inflammation and apoptosis and by interfering with glucose and lipid metabolism [58]. In a recent study, Ma et al. reported that liver-specific related protein 1 (DRP1) knockout (L-DRP1 KO) in mice led to reduced DRP1 expression levels and increased accumulation of giant mitochondria in the liver. RNA-seq and qPCR analysis revealed that the expression of genes related to the cGAS-STING-interferon pathway was increased in L-DRP1-KO mice, regardless of alcohol consumption. Moreover, alcohol-fed L-DRP1-KO mice exhibit increased cytoplasmic mtDNA levels, impaired mitochondrial function, increased activation of the cGAS-STING pathway, and subsequent liver injury [59]. The role of the cGAS-STING pathway in fatty liver disease (including NAFLD and ALD) has not been fully elucidated, but experimental results suggest that the cGAS-STING pathway could be a therapeutic target for treating fatty liver disease.

3.3. The cGAS-STING pathway in bone metabolism physiology and pathology

The skeleton provides structural support and protection, plays a role in calcium metabolism and endocrine control, and stimulates the haematopoietic system in the bone marrow. The perpetual process of bone remodelling largely relies on osteoclasts that absorb old bone and osteoblasts that build the new matrix and refine it. In adults, bone remodelling typically remains in a state of balance, known as bone homeostasis [60]. Disruption of these factors can lead to a decrease in bone quality and a decrease in bone mass, leading to osteoporosis. This common pathological mechanism is observed in various metabolic bone disorders. The receptor activator of nuclear factor-κB (RANK)-RANKL-OPG pathway, which plays a critical role in bone resorption, regulates osteoblast differentiation through a variety of pathways and transcription factors, in either a beneficial or detrimental way [61]. In recent years, the role of STING in bone metabolic disorders has become a major focus of attention. Osteoporosis is a bone metabolic disease characterised by aseptic inflammatory processes. Elevated levels of NF-κB, which promotes osteoclast-mediated bone resorption and suppresses osteoblast-induced bone formation, can be observed in osteoporosis models [62]. STING acts as an upstream regulator of NF-κB, stimulating its activation and transcription, thus mediating proinflammatory effects and playing a role in the pathogenesis of osteoporosis. Notably, IFN-β is also a downstream target of STING and can negatively regulate osteoclast activation through a feedback mechanism [63]. The above research findings indicate that the cGAS-STING pathway plays a significant role in the pathogenesis of osteoporosis. Therefore, targeting the cGAS-STING pathway could have potential in the treatment of osteoporosis.

3.4. The cGAS-STING pathway in neurodegenerative diseases

Aging is characterized by systemic chronic low-grade inflammation, accompanied by cellular senescence and immunosenescence. When cells become senescent, they produce cytokines, chemokines, growth factors, proteases, and angiogenic factors, which are characteristic of the senescence-associated secretory phenotype (SASP), along with the production of inflammatory responses, further promoting cellular senescence [64]. Immune cells, as key regulators of senescent cells, have been repeatedly shown to be related to cognitive processes and neurodegenerative diseases, most notably Alzheimer's disease (AD) and Parkinson's disease (PD) [65]. AD is an age-dependent, fatal neurodegenerative disorder, with mitochondrial dysfunction being one of the key pathophysiological mechanisms involved. Toxic protein aggregates such as amyloid-beta or hyperphosphorylated tau induce mtDNA oxidative damage and DNA double-strand breaks, with damaged DNA fragments released into the cytoplasm acting as ligands for cGAS, further activating STING and promoting neuroinflammatory responses [66]. Xie et al. found that 6-month-old 5xFAD mice have much higher levels of cytoplasmic mtDNA (cmtDNA) in their brain cells compared to wild-type (WT) mice, and that 20-month-old WT mice have higher levels of cmtDNA in their brain cells compared to 3-month-old mice. Further studies have shown significant increases in the levels of STING, TBK1, p-65, and phosphorylated IRF3 in the prefrontal cortex of humans with AD and in the cortex of aged mice [67]. PD is a neurodegenerative movement disorder characterized by the loss of substantia nigra neurons, leading to striatal dopamine deficiency [68]. Alex et al. found that STING protein levels in endothelial cells and neurons of PD patients were elevated compared to non-neurodegenerative control tissues, and they also observed the widespread presence of STING-positive neuronal cell bodies in the SnPC area of PD brain tissue [69].

In summary, these findings indicate that cGAS-STING signaling and neuroinflammatory responses are closely related to aging and neurodegenerative diseases, with microglia playing a crucial role.

4. Inhibitors of the cGAS-STING pathway

4.1. cGAS inhibitors

Continuous activation of cGAS, an intracellular DNA sensor, can potentially lead to various chronic metabolic disorders. Inhibiting its activation, as a key initiator in this pathway, could be a therapeutic approach for such diseases. Interfering with DNA binding to cGAS, disrupting ATP and GTP-cGAS interactions, and altering cGAS activity through posttranslational changes to its catalytic activity are all ways to impede cGAS activation. Previously, it was discovered that antimalarial drugs (AMDs), such as hydroxychloroquine and quinacrine, have inhibitory effects on cGAMP synthesis. Their mechanism of action involves binding to cytoplasmic DNA, thereby preventing the binding of DNA to cGAS [70]. Through high-throughput screening analysis, compounds such as RU.365 and its benzothiazole analogue RU.332 were found to exhibit inhibitory effects on mouse cGAS [71]. These compounds occupy the catalytic site of cGAS, thereby reducing the affinity of cGAS for ATP and GTP and consequently inhibiting the production of 2′,3′-cGAMP. The

chlorinated compound RU.521 can reduce the expression of IFN-β1 in mouse macrophages [71,72]. Posttranslational modifications are highly significant in regulating protein functionality. Aspirin, an acetyl donor, can increase cGAS acetylation and inhibit cGAS activity [73]. Hall and colleagues described the development of a high-affinity (KD = 200 nM) small molecule inhibitor, PF-06928215, and demonstrated its drug-like properties. This binding may impact the interaction between ATP and cGAS, as well as downstream cGAMP synthesis [74].

Research into the efficacy and safety of these inhibitors is ongoing, and further exploration is essential.

4.2. STING inhibitors

As a crucial signaling molecule bridging the cGAS-STING pathway, STING has been extensively studied for drug development in recent years. Research on STING inhibitors has focused primarily on the palmitoylation of STING. Mukai et al. [34] found that palmitoylation sites are located at cysteine 88/91 of the STING protein following STING activation. The palmitoylation of STING promotes its dimerisation and recruitment of downstream TBK1. Based on this discovery, researchers have developed compounds that target the cysteine 88 and 91 residues of the STING protein to inhibit protein palmitoylation. Additionally, compounds targeting other sites on the STING protein have been found to exhibit inhibitory effects. The cyclic peptide astin C, which is isolated from paclitaxel, prevents the recruitment of IRF3 by competitively binding to the activation pocket at the C-terminus of the STING protein, thereby inhibiting the innate immune response triggered by the cGAS-STING signalling pathway [75]. Moreover, Hansen et al. reported that endogenously formed nitro-fatty acids can covalently modify STING through nitroalkylation and subsequently suppress the release of type I IFN in human and mouse cells [76]. Recent research has shown that remdesivir can regulate hepatic cell lipid disorders and inflammation by inhibiting the expression of the STING gene, thereby alleviating high-fat diet-induced NAFLD [77].

Blocking cGAS-STING pathway activity may reduce the immune system's ability to detect tumour cells, thereby increasing the risk of tumour growth. It can also weaken antiviral and antibacterial responses, increasing the susceptibility of the body to severe infections [78–80]. The potential for these risks to impede the clinical utilisation of such drugs necessitates that they be accounted for during drug development. To validate these discoveries, preclinical studies and early clinical trials must be conducted. Recent advances in the development of STING inhibitors are summarized in Table 1.

Currently, agonists for the STING pathway are also being developed, primarily for the treatment of cancer, and the development of STING pathway agonists as cancer therapies predates the discovery of the STING pathway itself. Initial studies found that flavone acetic acid (FAA), as a vascular disrupting agent, showed potential as a cancer therapeutic agent [81]. Based on this, further optimized 5,6-dimethylxanthenone-4-acetic acid (DMXAA) exhibited potent anti-tumor activity in mouse tumor models [82], which is now known to involve STING activation. As research into the mechanism of the STING pathway deepened, the focus of STING-related agonist research shifted to STING's natural ligand cyclic dinucleotide (CDN) [83], and researchers are currently exploring synthetic STING small molecules. Similar to the development of STING inhibitors, research into the efficacy and safety of STING agonists is still ongoing, with Garland et al. providing a detailed review of the use of STING agonists in cancer therapy [84].

5. Discussion

Despite the discovery of the cGAS-STING signalling pathway being only in 2013, recent research has led to significant progress in understanding the mode of action of the DNA sensor cGAS, its crucial association with STING, and the role of the cGAS-STING signalling pathway in host defence and immunity. A recent study indicated that activation of the cGAS-STING pathway is closely associated with inflammation and immune regulation in metabolic disorders. Activation of the cGAS-STING pathway has been found to be a major factor in metabolic disorders, including obesity, insulin resistance, and fatty liver disease. Therefore, cGAS-STING plays a unique role in the development of metabolic diseases. Finding safe and effective methods to treat metabolic diseases remains a

Table 1
Inhibitors of STING protein.

STING inhibitors	Representative Compounds	Functions	note	References
Nitrofurans	C-178	Covalently binding with STING's Cys91 to block STING activation-induced palmitoylation.	Mouse-specific STING inhibitor.	[85]
Nitrofurans	C-176	Reducing the secretion of Type I interferons.	Mouse-specific STING inhibitor.	[86]
Indole derivatives	H-151	Binding to the Cys91 of STING		[87]
Oxo-tetrahydro-isoquinoline carboxylic acids	A series of tetrahydroisoquinolone analogs.	Competitive antagonist of cGAMP.		[88]
Multisubstituted benzamides or benzenesulfonamides.	A series of benzamides substituted with sulfonamide groups.	Inhibiting STING signaling transduction.		[89]
Cyclopeptides	astin C	Inhibiting intracellular DNA-induced Ifnb expression.		[90]
Dimeric benzimidazoles		Reducing the secretion of IFN.		[91]
Heterobicyclic derivatives		Inhibiting STING activity.		[92]
STING degraders	Proteolytic targeting chimera (PROTAC).	Recruiting E3 ubiquitin ligases to induce target protein degradation.		[93]

challenge. Notably, in a recent study on cancer metabolism in tumours, Liting Zhang and colleagues reported that STING limits aerobic glycolysis in tumours by inhibiting the activity of hexokinase II (HK2), thus enhancing antitumour immunity [94]. This innovative study suggested that STING acts as a metabolic checkpoint in cancer cells, highlighting its role in tumour biology. The development of therapeutic strategies and drugs targeting the cGAS-STING pathway is a significant challenge. Inhibiting the cGAS-STING pathway may have potential for treating metabolic disorders. Conversely, developing approaches targeting STING itself or promoting STING degradation is important for enhancing antitumour immunity and combating microbial pathogens. Hence, it is particularly important to identify drugs that allow for the selective modulation of cGAS-STING activity in various disease contexts. An in-depth understanding of the regulatory mechanisms of the cGAS-STING pathway is necessary to discover targetable effectors and to develop drugs that are both effective and safe. Targeting cGAS or STING has already been applied in antiviral immunotherapy and holds great promise as a novel therapeutic option in the field of metabolic disease treatment. In conclusion, these key discoveries and results offer significant insight into the role of the dsDNA pathway in metabolic disorders. Nevertheless, more research is required to probe the fundamental regulatory processes, interactions with other pathways, and potential therapeutic goals and tactics.

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Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Qian Xu: Writing – original draft, Formal analysis. **Jie Xing:** Software, Validation. **Shengjun Wang:** Conceptualization, Resources. **Huiyong Peng:** Writing – review & editing, Supervision, Funding acquisition. **Yingzhao Liu:** Writing – review & editing, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] A.M. Mahmoud, An Overview of epigenetics in obesity: the role of lifestyle and therapeutic interventions, Int. J. Mol. Sci. 23 (3) (Jan 25 2022).
[2] E. Maury, Off the clock: from circadian disruption to metabolic disease, Int. J. Mol. Sci. 20 (7) (Mar 30 2019).
[3] J. Tremblay, P. Hamet, Environmental and genetic contributions to diabetes, Metab., Clin. Exp. 100s (Nov 2019) 153952.
[4] K. Nakahira, S. Hisata, A.M. Choi, The roles of mitochondrial damage-associated molecular patterns in diseases, Antioxidants Redox Signal. 23 (17) (Dec 10 2015) 1329–1350.
[5] M. Motwani, S. Pesiridis, K.A. Fitzgerald, DNA sensing by the cGAS-STING pathway in health and disease, Nat. Rev. Genet. 20 (11) (Nov 2019) 657–674.
[6] L. Sun, J. Wu, F. Du, X. Chen, Z.J. Chen, Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway, Science (New York, N. Y.) 339 (6121) (Feb 15 2013) 786–791.
[7] K. Kato, H. Omura, R. Ishitani, O. Nureki, Cyclic GMP-AMP as an endogenous second messenger in innate immune signaling by cytosolic DNA, Annu. Rev. Biochem. 86 (Jun 20 2017) 541–566.
[8] X.M. Ma, K. Geng, B.Y. Law, et al., Lipotoxicity-induced mtDNA release promotes diabetic cardiomyopathy by activating the cGAS-STING pathway in obesity-related diabetes, Cell Biol. Toxicol. 39 (1) (Feb 2023) 277–299.
[9] S.E. Elzinga, E.J. Koubek, J.M. Hayes, et al., Modeling the innate inflammatory cGAS/STING pathway: sexually dimorphic effects on microglia and cognition in obesity and prediabetes, Front. Cell. Neurosci. 17 (2023) 1167688.
[10] H. Gao, Z. Luo, Y. Ji, et al., Accumulation of microbial DNAs promotes to islet inflammation and β cell abnormalities in obesity in mice, Nat. Commun. 13 (1) (Jan 28 2022) 565.
[11] X. Luo, H. Li, L. Ma, et al., Expression of STING is increased in liver tissues from patients with NAFLD and promotes macrophage-mediated hepatic inflammation and fibrosis in mice, Gastroenterology 155 (6) (Dec 2018) 1971–1984.e1974.
[12] Y. Yu, Y. Liu, W. An, J. Song, Y. Zhang, X. Zhao, STING-mediated inflammation in Kupffer cells contributes to progression of nonalcoholic steatohepatitis, J. Clin. Invest. 129 (2) (Feb 1 2019) 546–555.
[13] Z. Gao, Z. Gao, H. Zhang, S. Hou, Y. Zhou, X. Liu, Targeting STING: from antiviral immunity to treat osteoporosis, Front. Immunol. 13 (2022) 1095577.
[14] X. Li, C. Shu, G. Yi, et al., Cyclic GMP-AMP synthase is activated by double-stranded DNA-induced oligomerization, Immunity 39 (6) (Dec 12 2013) 1019–1031.
[15] W. Zhou, A.T. Whiteley, C.C. de Oliveira Mann, et al., Structure of the human cGAS-DNA complex reveals enhanced control of immune surveillance, Cell 174 (2) (Jul 12 2018) 300–311.e311.
[16] S. Luecke, A. Holleufer, M.H. Christensen, et al., cGAS is activated by DNA in a length-dependent manner, EMBO Rep. 18 (10) (Oct 2017) 1707–1715.
[17] K.C. Barnett, J.M. Coronas-Serna, W. Zhou, et al., Phosphoinositide interactions position cGAS at the plasma membrane to ensure efficient distinction between self- and viral DNA, Cell 176 (6) (Mar 7 2019) 1432–1446.e1411.

[18] M. Gentili, X. Lahaye, F. Nadalin, et al., The N-terminal domain of cGAS determines preferential association with centromeric DNA and innate immune activation in the nucleus, Cell Rep. 26 (9) (Feb 26 2019) 2377–2393.e2313.
[19] H.E. Volkman, S. Cambier, E.E. Gray, D.B. Stetson, Tight nuclear tethering of cGAS is essential for preventing autoreactivity, Elife 8 (Dec 6 2019).
[20] S.L. Ergun, D. Fernandez, T.M. Weiss, L. Li, STING polymer structure reveals mechanisms for activation, hyperactivation, and inhibition, Cell 178 (2) (Jul 11 2019) 290–301.e210.
[21] S. Ouyang, X. Song, Y. Wang, et al., Structural analysis of the STING adaptor protein reveals a hydrophobic dimer interface and mode of cyclic di-GMP binding, Immunity 36 (6) (Jun 29 2012) 1073–1086.
[22] C. Shu, G. Yi, T. Watts, C.C. Kao, P. Li, Structure of STING bound to cyclic di-GMP reveals the mechanism of cyclic dinucleotide recognition by the immune system, Nat. Struct. Mol. Biol. 19 (7) (Jun 24 2012) 722–724.
[23] C. Zhang, G. Shang, X. Gui, X. Zhang, X.C. Bai, Z.J. Chen, Structural basis of STING binding with and phosphorylation by TBK1, Nature 567 (7748) (Mar 2019) 394–398.
[24] L.D. Aarreberg, K. Esser-Nobis, C. Driscoll, A. Shuvarikov, J.A. Roby, M. Gale Jr., Interleukin-1β induces mtDNA release to activate innate immune signaling via cGAS-STING, Mol. Cell 74 (4) (May 16 2019) 801–815, e806.
[25] C. Zierhut, H. Funabiki, Regulation and consequences of cGAS activation by self-DNA, Trends Cell Biol. 30 (8) (Aug 2020) 594–605.
[26] A.M. Herzner, C.A. Hagmann, M. Goldeck, et al., Sequence-specific activation of the DNA sensor cGAS by Y-form DNA structures as found in primary HIV-1 cDNA, Nat. Immunol. 16 (10) (Oct 2015) 1025–1033.
[27] A. Ablasser, M. Goldeck, T. Cavlar, et al., cGAS produces a 2'-5'-linked cyclic dinucleotide second messenger that activates STING, Nature 498 (7454) (Jun 20 2013) 380–384.
[28] K.P. Hopfner, V. Hornung, Molecular mechanisms and cellular functions of cGAS-STING signalling, Nat. Rev. Mol. Cell Biol. 21 (9) (Sep 2020) 501–521.
[29] W. Xie, D.J. Patel, Structure-based mechanisms of 2'3'-cGAMP intercellular transport in the cGAS-STING immune pathway, Trends Immunol. 44 (6) (Jun 2023) 450–467.
[30] A. Ablasser, J.L. Schmid-Burgk, I. Hemmerling, et al., Cell intrinsic immunity spreads to bystander cells via the intercellular transfer of cGAMP, Nature 503 (7477) (Nov 28 2013) 530–534.
[31] R.D. Luteijn, S.A. Zaver, B.G. Gowen, et al., SLC19A1 transports immunoreactive cyclic dinucleotides, Nature 573 (7774) (Sep 2019) 434–438.
[32] L.J. Lahey, R.E. Mardjuki, X. Wen, et al., LRRC8A:C/E heteromeric channels are ubiquitous transporters of cGAMP, Mol. Cell 80 (4) (Nov 19 2020) 578–591.e575.
[33] X. Wei, L. Zhang, Y. Yang, et al., LL-37 transports immunoreactive cGAMP to activate STING signaling and enhance interferon-mediated host antiviral immunity, Cell Rep. 39 (9) (May 31 2022) 110880.
[34] K. Mukai, H. Konno, T. Akiba, et al., Activation of STING requires palmitoylation at the Golgi, Nat. Commun. 7 (Jun 21 2016) 11932.
[35] S. Liu, X. Cai, J. Wu, et al., Phosphorylation of innate immune adaptor proteins MAVS, STING, and TRIF induces IRF3 activation, Science (New York, N.Y.) 347 (6227) (Mar 13 2015) aaa2630.
[36] B. Zhao, C. Shu, X. Gao, et al., Structural basis for concerted recruitment and activation of IRF-3 by innate immune adaptor proteins, Proc. Natl. Acad. Sci. U.S.A. 113 (24) (Jun 14 2016) E3403–E3412.
[37] T. Tsuchida, J. Zou, T. Saitoh, et al., The ubiquitin ligase TRIM56 regulates innate immune responses to intracellular double-stranded DNA, Immunity 33 (5) (Nov 24 2010) 765–776.
[38] D. Liu, H. Wu, C. Wang, et al., STING directly activates autophagy to tune the innate immune response, Cell Death Differ. 26 (9) (Sep 2019) 1735–1749.
[39] D. Prantner, D.J. Perkins, S.N. Vogel, AMP-Activated kinase (AMPK) promotes innate immunity and antiviral defense through modulation of stimulator of interferon genes (STING) signaling, J. Biol. Chem. 292 (1) (Jan 6 2017) 292–304.
[40] J.S. Harrington, S.W. Ryter, M. Plataki, D.R. Price, A.M.K. Choi, Mitochondria in health, disease, and aging, Physiol. Rev. 103 (4) (Oct 1 2023) 2349–2422.
[41] P. Andrieux, C. Chevillard, E. Cunha-Neto, J.P.S. Nunes, Mitochondria as a cellular hub in infection and inflammation, Int. J. Mol. Sci. 22 (21) (Oct 20 2021).
[42] J.R. Yarbro, R.S. Emmons, B.D. Pence, Macrophage immunometabolism and inflammaging: roles of mitochondrial dysfunction, cellular senescence, CD38, and NAD, Immunometabolism 2 (3) (2020) e200026.
[43] J. Bai, C. Cervantes, J. Liu, et al., DsbA-L prevents obesity-induced inflammation and insulin resistance by suppressing the mtDNA release-activated cGAS-cGAMP-STING pathway, Proc. Natl. Acad. Sci. U.S.A. 114 (46) (Nov 14 2017) 12196–12201.
[44] L. Andreeva, B. Hiller, D. Kostrewa, et al., cGAS senses long and HMGB/TFAM-bound U-turn DNA by forming protein-DNA ladders, Nature 549 (7672) (Sep 21 2017) 394–398.
[45] K.W. Chung, P. Dhillon, S. Huang, et al., Mitochondrial damage and activation of the STING pathway lead to renal inflammation and fibrosis, Cell Metabol. 30 (4) (Oct 1 2019) 784–799.e785.
[46] A.P. West, W. Khoury-Hanold, M. Staron, et al., Mitochondrial DNA stress primes the antiviral innate immune response, Nature 520 (7548) (Apr 23 2015) 553–557.
[47] E. Vringer, S.W.G. Tait, Mitochondria and cell death-associated inflammation, Cell Death Differ. 30 (2) (Feb 2023) 304–312.
[48] K. McArthur, L.W. Whitehead, J.M. Heddleston, et al., BAK/BAX macropores facilitate mitochondrial herniation and mtDNA efflux during apoptosis, Science (New York, N.Y.) 359 (6378) (Feb 23 2018).
[49] H. Xian, K. Watari, E. Sanchez-Lopez, et al., Oxidized DNA fragments exit mitochondria via mPTP- and VDAC-dependent channels to activate NLRP3 inflammasome and interferon signaling, Immunity 55 (8) (Aug 9 2022) 1370–1385.e1378.
[50] C.H. Yu, S. Davidson, C.R. Harapas, et al., TDP-43 triggers mitochondrial DNA release via mPTP to activate cGAS/STING in ALS, Cell 183 (3) (Oct 29 2020) 636–649.e618.
[51] T. Kawai, M.V. Autieri, R. Scalia, Adipose tissue inflammation and metabolic dysfunction in obesity, Am. J. Physiol. Cell Physiol. 320 (3) (Mar 1 2021) C375–c391.
[52] W. Ying, W. Fu, Y.S. Lee, J.M. Olefsky, The role of macrophages in obesity-associated islet inflammation and β-cell abnormalities, Nat. Rev. Endocrinol. 16 (2) (Feb 2020) 81–90.
[53] H. Wu, Y. Wang, W. Li, et al., Deficiency of mitophagy receptor FUNDC1 impairs mitochondrial quality and aggravates dietary-induced obesity and metabolic syndrome, Autophagy 15 (11) (Nov 2019) 1882–1898.
[54] V.H. Cruz, E.N. Arner, K.W. Wynne, P.E. Scherer, R.A. Brekken, Loss of Tbk1 kinase activity protects mice from diet-induced metabolic dysfunction, Mol. Metabol. 16 (Oct 2018) 139–149.
[55] X. Gui, H. Yang, T. Li, et al., Autophagy induction via STING trafficking is a primordial function of the cGAS pathway, Nature 567 (7747) (Mar 2019) 262–266.
[56] E.A. Oral, S.M. Reilly, A.V. Gomez, et al., Inhibition of IKKε and TBK1 improves glucose control in a subset of patients with type 2 diabetes, Cell Metabol. 26 (1) (Jul 5 2017) 157–170.e157.
[57] A.J. Sanyal, Past, present and future perspectives in nonalcoholic fatty liver disease, Nat. Rev. Gastroenterol. Hepatol. 16 (6) (Jun 2019) 377–386.
[58] J.T. Qiao, C. Cui, L. Qing, et al., Activation of the STING-IRF3 pathway promotes hepatocyte inflammation, apoptosis and induces metabolic disorders in nonalcoholic fatty liver disease, Metab., Clin. Exp. 81 (Apr 2018) 13–24.
[59] X. Ma, A. Chen, L. Melo, et al., Loss of hepatic DRP1 exacerbates alcoholic hepatitis by inducing megamitochondria and mitochondrial maladaptation, Hepatology 77 (1) (Jan 1 2023) 159–175.
[60] J.M. Kim, C. Lin, Z. Stavre, M.B. Greenblatt, J.H. Shim, Osteoblast-osteoclast communication and bone homeostasis, Cells 9 (9) (Sep 10 2020).
[61] N.E. McGregor, M. Murat, J. Elango, et al., IL-6 exhibits both cis- and trans-signaling in osteocytes and osteoblasts, but only trans-signaling promotes bone formation and osteoclastogenesis, J. Biol. Chem. 294 (19) (May 10 2019) 7850–7863.
[62] T.H. Lin, J. Pajarinen, L. Lu, et al., NF-κB as a therapeutic target in inflammatory-associated bone diseases, Advances in protein chemistry and structural biology 107 (2017) 117–154.
[63] Z. Yao, S.J. Getting, I.C. Locke, Regulation of TNF-induced osteoclast differentiation, Cells 11 (1) (Dec 31 2021).

[64] Q. Cai, Y.Y. Jeong, Mitophagy in Alzheimer's disease and other age-related neurodegenerative diseases, Cells 9 (1) (Jan 8 2020).
[65] A. Jauhari, S.V. Baranov, Y. Suofu, et al., Melatonin inhibits cytosolic mitochondrial DNA-induced neuroinflammatory signaling in accelerated aging and neurodegeneration, J. Clin. Invest. 130 (6) (Jun 1 2020) 3124–3136.
[66] G.E. Moya, P.D. Rivera, K.E. Dittenhafer-Reed, Evidence for the role of mitochondrial DNA release in the inflammatory response in neurological disorders, Int. J. Mol. Sci. 22 (13) (Jun 29 2021).
[67] X. Xie, G. Ma, X. Li, J. Zhao, Z. Zhao, J. Zeng, Activation of innate immune cGAS-STING pathway contributes to Alzheimer's pathogenesis in 5×FAD mice, Nature aging 3 (2) (Feb 2023) 202–212.
[68] S.Y. Jiang, T. Tian, H. Yao, et al., The cGAS-STING-YY1 axis accelerates progression of neurodegeneration in a mouse model of Parkinson's disease via LCN2-dependent astrocyte senescence, Cell Death Differ. 30 (10) (Oct 2023) 2280–2292.
[69] A.S. Ferecskó, M.J. Smallwood, A. Moore, et al., STING-triggered CNS inflammation in human neurodegenerative diseases, Biomedicines 11 (5) (May 5 2023).
[70] J. An, M. Minie, T. Sasaki, J.J. Woodward, K.B. Elkon, Antimalarial drugs as immune modulators: new mechanisms for old drugs, Annu. Rev. Med. 68 (Jan 14 2017) 317–330.
[71] J. Vincent, C. Adura, P. Gao, et al., Small molecule inhibition of cGAS reduces interferon expression in primary macrophages from autoimmune mice, Nat. Commun. 8 (1) (Sep 29 2017) 750.
[72] C. Wiser, B. Kim, J. Vincent, M. Ascano, Small molecule inhibition of human cGAS reduces total cGAMP output and cytokine expression in cells, Sci. Rep. 10 (1) (May 5 2020) 7604.
[73] J. Dai, Y.J. Huang, X. He, et al., Acetylation blocks cGAS activity and inhibits self-DNA-induced autoimmunity, Cell 176 (6) (Mar 7 2019) 1447–1460.e1414.
[74] J. Hall, A. Brault, F. Vincent, et al., Discovery of PF-06928215 as a high affinity inhibitor of cGAS enabled by a novel fluorescence polarization assay, PLoS One 12 (9) (2017) e0184843.
[75] S. Li, Z. Hong, Z. Wang, et al., The cyclopeptide astin C specifically inhibits the innate immune CDN sensor STING, Cell Rep. 25 (12) (Dec 18 2018) 3405–3421.e3407.
[76] A.L. Hansen, G.J. Buchan, M. Rühl, et al., Nitro-fatty acids are formed in response to virus infection and are potent inhibitors of STING palmitoylation and signaling, Proc. Natl. Acad. Sci. U.S.A. 115 (33) (Aug 14 2018) E7768–e7775.
[77] Y.N. Li, Y. Su, Remdesivir attenuates high fat diet (HFD)-induced NAFLD by regulating hepatocyte dyslipidemia and inflammation via the suppression of STING, Biochem. Biophys. Res. Commun. 526 (2) (May 28 2020) 381–388.
[78] L. Gao, R. Liu, F. Yang, et al., Duck enteritis virus inhibits the cGAS-STING DNA-sensing pathway to evade the innate immune response, J. Virol. 96 (24) (Dec 21 2022) e0157822.
[79] K. Li, Y. Liu, Z. Xu, et al., Avian oncogenic herpesvirus antagonizes the cGAS-STING DNA-sensing pathway to mediate immune evasion, PLoS Pathog. 15 (9) (Sep 2019) e1007999.
[80] M. Peng, X. Li, X. Zhang, L. Peng, Inhibition of cGAS aggravated the host inflammatory response to Aspergillus fumigatus, Exp. Lung Res. 49 (1) (2023) 86–100.
[81] G.P. Smith, S.B. Calveley, M.J. Smith, B.C. Baguley, Flavone acetic acid (NSC 347512) induces haemorrhagic necrosis of mouse colon 26 and 38 tumours, Eur. J. Cancer Clin. Oncol. 23 (8) (Aug 1987) 1209–1211.
[82] S. Kim, L. Li, Z. Maliga, Q. Yin, H. Wu, T.J. Mitchison, Anticancer flavonoids are mouse-selective STING agonists, ACS Chem. Biol. 8 (7) (Jul 19 2013) 1396–1401.
[83] Z. Hong, J. Mei, C. Li, et al., STING inhibitors target the cyclic dinucleotide binding pocket, Proc. Natl. Acad. Sci. U.S.A. 118 (24) (Jun 15 2021).
[84] K.M. Garland, T.L. Sheehy, J.T. Wilson, Chemical and biomolecular strategies for STING pathway activation in cancer immunotherapy, Chem. Rev. 122 (6) (Mar 23 2022) 5977–6039.
[85] A.L. Fryer, A. Abdullah, F. Mobilio, et al., Pharmacological inhibition of STING reduces neuroinflammation-mediated damage post-traumatic brain injury, Br. J. Pharmacol. (2024 May 2024).
[86] Y. Fujita, 2-Nitrofuran Arylamide Compounds As Innate Immune Modulators, 2019.
[87] P.W. Chang, J.Y. Wang, W.P. Wang, et al., Analysis of structure-activity relationship of indol-3-yl-N-phenylcarbamic amides as potent STING inhibitors, Bioorg. Med. Chem. 95 (Nov 15 2023) 117502.
[88] C. Ding, Z. Song, A. Shen, T. Chen, A. Zhang, Small molecules targeting the innate immune cGAS–STING–TBK1 signaling pathway, Acta Pharm. Sin. 10 (12) (2020) 2272–2298. B. Dec.
[89] J.W. Pei, Y.B. Zhang, Q.H. Luo, et al., STAT3 inhibition enhances CDN-induced STING signaling and antitumor immunity, Cancer Lett. 450 (2019) 110–122.
[90] X. Wang, Y. Wang, A. Cao, et al., Development of cyclopeptide inhibitors of cGAS targeting protein-DNA interaction and phase separation, Nat. Commun. 14 (1) (Oct 2 2023).
[91] Z. Song, X. Wang, Y. Zhang, et al., Structure-activity relationship study of amidobenzimidazole analogues leading to potent and systemically administrable stimulator of interferon gene (STING) agonists, J. Med. Chem. 64 (3) (Feb 11 2021) 1649–1669.
[92] D. Cai, H. Liu, J. Wang, et al., Balasubramide derivative 3C attenuates atherosclerosis in apolipoprotein E-deficient mice: role of AMPK-STAT1-STING signaling pathway, Aging 13 (8) (Apr 26 2021) 12160–12178.
[93] Z. Zhu, R.L. Johnson, Z. Zhang, et al., Development of VHL-recruiting STING PROTACs that suppress innate immunity, Cell. Mol. Life Sci. : CM 80 (6) (May 14 2023) 149.
[94] L. Zhang, C. Jiang, Y. Zhong, et al., STING is a cell-intrinsic metabolic checkpoint restricting aerobic glycolysis by targeting HK2, Nat. Cell Biol. 25 (8) (Aug 2023) 1208–1222.