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Cardiovascular diseases crossroads: cGAS-STING signaling and disease progression

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ABSTRACT

It is now widely accepted that inflammation is critical in cardiovascular diseases (CVD). Here, studies are being conducted on how cyclic GMP-AMP synthase (cGAS), a component of innate immunity's DNA-sensing machinery, communicates with the STING receptor, which is involved in activating the immune system's antiviral response. Significantly, a growing body of research in recent years highlights the strong activation of the cGAS-STING signalling pathways in several cardiovascular diseases, such as myocardial infarction, heart failure, and myocarditis. This developing collection of research emphasises these pathways' crucial role in initiating and advancing cardiovascular disease. In this extensive narrative, we explore the role of the cGAS-STING pathway in the development of CVD. We elaborate on the basic mechanisms involved in the onset and progression of CVD. This review explores the most recent developments in the recognition and characterization of cGAS-STING pathway. Additionally, it considers the field's future prospects while examining how cGAS-STING pathway might be altered and its clinical applications for cardiovascular diseases.

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Introduction

Cardiovascular diseases (CVDs) cover a diverse range of complex ailments. The conditions above encompass cardiomyopathies, congenital cardiac anomalies, thoracic aortic aneurysms, coronary artery pathologies, and heart failure (HF). The complex circumstances mentioned above substantially impact fatalities worldwide.[1–4] Despite significant progress in pharmacology and surgery, improving outcomes, and increased survival rates for persons with cardiovascular diseases (CVDs), the overall outlook for these conditions remains discouraging.[5] Numerous research efforts have shown the significance of genetic variables and their expression profile modifications as the primary catalysts of genetic components and pathological cardiac events.[6] Cardiovascular diseases (CVDs) are a prominent contributor to morbidity and mortality on a global scale, encompassing disorders such as myocardial infarction (MI) and cardiomyopathy that impact individuals across various age cohorts. Globally, the annual mortality rate due to cardiovascular diseases (CVDs) exceeds 17 million individuals.[7] Despite the considerable progress made in medical therapies, there is still a lack of comprehensive exploration of techniques specifically targeting individual molecules.[8–10] In contrast to several other cellular populations, the heart has an inherent deficiency in regenerative capacity following substantial injury, such as ischemic events. Restoring myocardial function is a substantial difficulty. Different types of cell death have distinct functions in different situations. These include established pathways such as apoptosis, autophagy, and proptosis, as well as emerging processes like ferroptosis, which is thought to be significant in the progression of several diseases, including cardiac problems.[11–13]

Moreover, cardiac ageing is widely recognized as a significant determinant of heart disease, wherein cellular senescence plays a crucial role in driving this occurrence.[14] Although the precise mechanisms responsible for heart illness are not yet fully understood, there is a strong association between mitochondrial malfunction and cardiac injury.[15,16] Senescent cells accumulate in an ageing heart and trigger inflammation by producing chemokines and cytokines called the senescence-associated secretory phenotype. Inflammation's part in the aetiology of some cardiovascular diseases is now generally recognized.[17,18] The cyclic GMP-AMP synthase and activator of interferon genes pathway stimulates downstream cytokines, interleukin (IL), tumour necrosis factor (TNF), and other inflammatory agents such as interleukin (IL) and IL.[19] Extensive research has been done to investigate its engagement in various cellular activities and its well-documented roles in immune response and inflammatory processes. In addition to controlling senescence, the cGAS-STING signalling pathway controls the senescence-associated secretory phenotype.[20] Mitochondrial DNA in the cytoplasm may activate the cGAS-STING pathway by interacting with cGAS.[21]

Therefore, this pathway controls the senescence-associated secretory phenotype, which leads to the activation of the inflammatory response. Moreover, it is linked to other biological processes like autophagy, proptosis, apoptosis, and ferroptosis [22–26] Noteworthy is that prior research suggests that a breakdown of the cGAS-STING pathway is responsible for various disordered cardiac activities[27,28], while several mediating pathways still need to be discovered (Table 1). Significantly, prior research has indicated that disturbances in the cGAS-STING pathway are involved in several cardiac dysfunctions; however, specific underlying processes have yet to be fully elucidated.[29]About the diverse range of roles played by the cGAS-STING pathway in cardiac diseases, there has been a growing interest in exploring various drug-like molecules.[30] The substances above have exhibited encouraging outcomes in controlled laboratory settings and animal experimentation, presenting prospective paths for advancing clinical interventions. Given the data above, the

Table 1
The connection between cardiac dysfunction and the cGAS-STING pathway.

Cardiovascular Disorder	*In vivo* or *in vitro*	Administration and cGAS-STING Pathway	Effect	Potential methods	Refs.
MI	Mouse model of myocardial infarction, fibroblasts, cardiomyocytes, and cardiac.	Reducing STING Activity with H-151	lowered myocardial fibrosis and apoptosis and preserved myocardial function	Apoptosis inhibition	[28]
SIC	LPS-treated NRCMs and LPS-induced mice	Using siRNA, we can knock down or knock out STING.	Enhanced cardiac performance; decreased myocardial inflammation, apoptosis, and pyroptosis; slowed cell death	Reducing apoptosis and pyroptosis by inhibiting the NLRP3 inflammasome	[43]
MI	Macrophage infarction (MI) model mice	siRNA knockdown of cGAS or STING	Enhance heart function and reduce inflammation.	Undefined	[44]
DCM	Neonatal mouse cardiomyocytes (NMCMs), the DCM mouse model, and isolated H9C2 cardiomyocytes	cGAS siRNA knockdown	In DCM mice, it reduced myocardial pyroptosis, inflammation, and enhanced heart function, reducing diabetes-induced hypertrophy	Autophagy restoration	[45]
MI	MI-murine model	STING inhibition with H-151	ReducedThe results were infarct size and scarring, enhanced left ventricular systolic performance, and mitigated myocardial hypertrophy.	Undefined	[46]
LIC	Palmitic acid challenges neonatal rat cardiomyocytes (NRCMs)	Selective genetic suppression of cGAS, STING, and IRF3	Improved NRCM viability	Minimizing NLRP3 inflammation	[47]
DCM	Mice with DCM and H9C2 cells exposed to PA.	Inhibition of STING by C-176	Minimized inflammation and apoptosis.	Disrupting cytosolic mtDNA and inflammation	[48]
High-pressure overload (HF)	Mice with transverse aortic constriction	SIRNA-induced cGAS knockdown	Impaired cardiac remodeling and maintained LV function.	Reducing inflammation and apoptosis	[49]

potential utilization of the cGAS-STING pathway emerges as a prospective focus for advancing therapeutic interventions to enhance cardiac well-being.[31]

Recent research has shown that treating cardiovascular conditions like myocardial infarction and heart failure with medications like angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACE inhibitors), and aldosterone receptor blockers significantly reduces mortality and readmission rates associated with these diseases.[32–36] Additionally, the strategic use of β-adrenergic receptor blockers and angiotensin receptor enkeenase inhibitors, which possess the combined effect of angiotensin II receptor blockade and elevation of natriuretic peptide levels, has contributed significantly to these positive outcomes. However, it is essential to note that cardiovascular disease (CVD) constituted approximately 32 % of the total global mortality rate in 2017.[37] Hence, addressing the reduction of cardiovascular illnesses, slowing the progression of cardiovascular diseases, and enhancing the prognosis of individuals afflicted with cardiovascular diseases remains a significant global public health challenge that necessitates resolution. cGAS, also known as MB21D1, is an enzyme that detects double-stranded DNA. When cGAS attaches to DNA, it activates and produces cyclic GMP-AMP (cGAMP). This molecule initiates the interferon gene (STING) as a second messenger. It has a unique and vital role in the host's defence against infections, immunity against tumours, autoimmune diseases, and age-related inflammation.[38–40] Heart failure and myocardial infarction (MI) are two cardiovascular illnesses for which the role of inflammatory variables and mediators in their development has been well established.[41,42] In recent years, the cGAS-STING signalling pathway has been highly active in myocardial infarction and heart failure. The cGAS-STING signalling pathway has been hypothesised to have a crucial role in the aetiology and development of cardiovascular disorders. Therefore, expanding our knowledge of the cGAS-STING signalling pathway in the cardiovascular system could lead to identifying new therapeutic targets for heart disorders. This article provides a comprehensive overview of cyclic GMP-AMP synthase and the cGAS-stimulator of interferon genes (STING) pathway, including their biochemical properties and the signalling cascade they support. It also delves into how cGAS affects the cardiovascular system.

The biochemical and structural features of cGAS

Overview of cGAS

The cGAS in the cytoplasm, plasma membrane, and nucleus functions as a specific DNA sensor. In terms of its composition, the protein consists of 522 amino acids and is classified under the nucleotidyl transferase (NTase) family. The protein under consideration comprises two discrete domains: a globular C-terminal domain that exhibits a high degree of conservation and an N-terminal domain that displays comparatively lower conservation. The N-terminal domain of cGAS is of significant importance in regulating its activity, as it either stabilises the protein or functions as an autoinhibitory component. Additionally, it aids in the formation of complexes between double-stranded DNA molecules.[27,50] Upon encountering extracellular dsDNA not localised in its designated region, the cyclic GMP-AMP synthase (cGAS) initiates a metabolic cascade, producing cyclic dinucleotide GMP-AMP (cGAMP). Canonical signalling

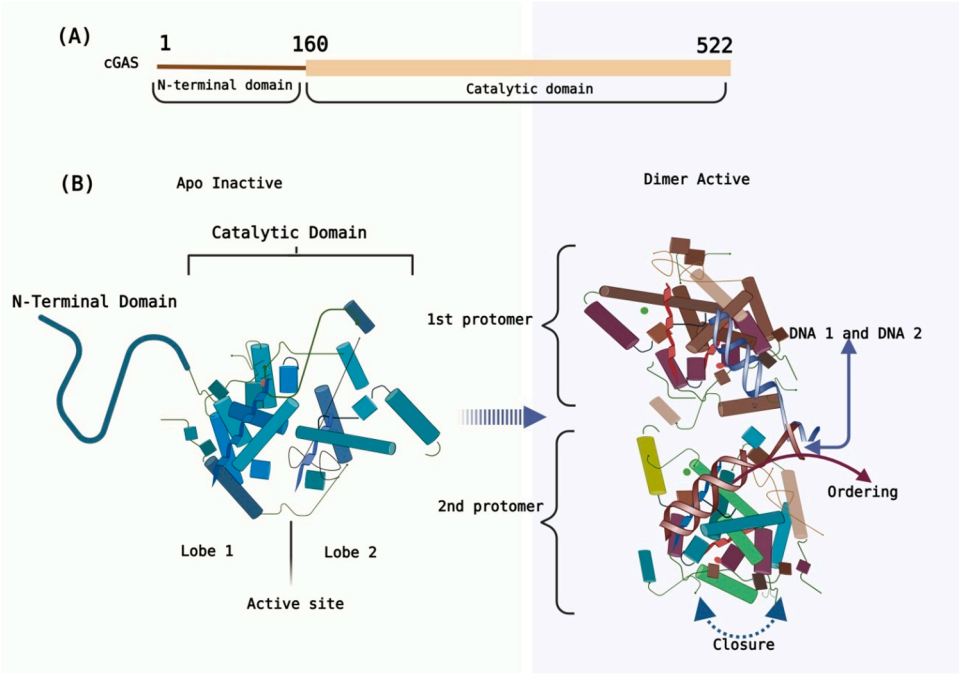

Fig. 1. The cGAS enzyme has a structural organization consisting of an N-terminal and catalytic domain. In its active form, it binds to DNA, dimerizes, and orders the activation loops, which causes the active site channel to close.

pathways are then set in the downstream direction.[51]

cGAS Structure

The human cGAS gene is located on chromosomal region 6q13. The mature cGAS protein contains 522 amino acids and interacts with the cell membrane through a region of 160 amino acids at its N-terminus. The protein contains a nucleotide transferase domain with a two-lobe structure and 362 amino acids. Fig. 1 shows the catalytic area in the interlobar grooves.[52,53] There are two DNA-binding sites on the surface of each cGAS molecule, which have been given the designations sites A and B. Site A plays a significant role in the conformational change following cGAS binding to DNA.

In contrast, site B is mainly involved in co-associating the cGAS dimer and DNA.[54] When cGAS comes into contact with dsDNA, it undergoes a conformational change, creating a dimeric complex that includes both cGAS and dsDNA. Experimentally, dsDNA is linked with site A of one cyclic GMP-AMP synthase (cGAS) molecule and site B of another cGAS molecule to produce a dimeric complex.[55] Recent scientific research has uncovered an extra binding site on the surface of cGAS, dubbed the C site. The activation of cGAS follows its dimerization, and it has been shown that this particular C site plays a crucial role in this process.[56]

Overview of STING

STING is predominantly localized to the endoplasmic reticulum (ER). Transmembrane protein 173 (TMEM173), novel plasma membrane tetraspanin (MPYS), and Endoplasmic Reticulum IFN Stimulator are some of their alternative names.[57] This entity has a C-terminal domain and 4 transmembrane domains (TM) that comprise its structural makeup. The C-terminal tail (CTT), C-binding domain, and ligand-binding domain (LBD) are the three individual parts that make up the C-terminal domain. The CTT can establish interactions with cyclic dinucleotides and promote downstream signalling cascades because of its propensity to form dimers in solution.[58]

STING maintains its ER attachment by interactions with several retainers, most notably Stromal Interaction Molecule 1. The STING protein leaves the endoplasmic reticulum (ER) after establishing a complex with complement-dependent neutrophils (CDNs). It moves to the ER-Golgi intermediate compartment (ERGIC)—several molecules linked to the coatomer protein complex II aid translocation.[59]

Localization of cGAS cells

Based on available data, cGAS has been reported to be distributed across many cellular compartments, including the cytoplasm, nucleus, and the cytoplasmic side of the cell membrane. Researchers discovered that cytoplasmic DNA can stimulate the production of type I interferon through a mechanism independent of toll-like receptor activation.[60] The authors later presented the innovative notion of a "cytoplasmic DNA sensor," which pertains to the involvement of the nuclear membrane in categorising the innate immune recognition receptors that target particular DNA molecules found within the cytoplasm. To accomplish targeted binding to cytoplasmic DNA while minimising interaction with endogenous genomic DNA. The initial discovery of cGAS as a constituent of the nucleotide transferase enzyme superfamily and its role as a "cytoplasmic DNA sensor" in initiating type I interferon synthesis 2013. The finding above was achieved using the processes of isolation, extraction, and quantitative mass spectrometry. Nevertheless, the notion of a "cytoplasmic DNA receptor" remains a subject of ongoing debate and disagreement among the academic community. cGAS is highly present in the nucleus of various cell types, including macrophages, human myeloid leukaemia mononuclear cells (THP-1), human embryonic kidney cells, and cervical cancer cells in humans.[61] In addition, except for poxviruses, the reproduction process for most DNA viruses takes place inside the nucleus. Inhibiting viral replication in the nucleus requires activating cyclic GMP-AMP synthase (cGAS) to elicit a type I interferon-mediated antiviral response. Studies using cGAS knockout mice have supported this phenomenon.[62,63] How can cGAS avoid attaching to its DNA or becoming inactive in the nucleus under normal conditions? Recent studies have shown that cyclic GMP-AMP synthase (cGAS) activity is significantly reduced by a nuclear component called the nucleosome core particle (NCP). Several pathways that prevent cyclic GMP-AMP synthase (cGAS) from being activated through competitive inhibition have been uncovered. The nucleocapsid protein (NCP) can occupy sites A or B, CGAS-NCP chains can form at sites B and C to prevent cGAS from binding to DNA, and cGAS dimerization can be blocked.[64]

According to recent investigations,cGAS, a protein implicated in the immune response, has been shown to relocate to the inner side of the cell membrane in various cell types, including THP-1 and immortalized bone marrow-derived macrophages. 4, 5-diphosphate interacts with the N-terminal region of cGAS, facilitating its localization. Furthermore, it has been observed that cGAS lacking the N-terminal region exhibits enhanced reactivity towards its DNA. A diminished responsiveness towards DNA from the poxvirus has been observed.[65,66] It is widely acknowledged among scholars that the placement of cGAS in the cell membrane isolates it from endogenous DNA and facilitates its prompt and efficient interaction with viral DNA.

cGAS post-translational modification

Accurate regulation of cGAS activity can be achieved through many processes, including proteolysis, ubiquitination, glutamylation, acetylation, methylation, SUMO, and phosphorylation. Other study demonstrated that a mass spectrometry investigation was performed on GFP-cGAS.[67] The results revealed the presence of six phosphorylation sites and eight acetylation sites inside GFP-cGAS. Notably, it was observed that phosphorylation at the S305 sites and acetylation at the K384 and K414 sites could impede Cgas-dependent apoptosis. Nevertheless, the process of acetylation at the K198 site facilitates the synthesis of cytokines. In their study,

Scientists discovered that acetylating aspirin can hinder the activation of cGAS.[68] In mice lacking the TREX1 gene, this inhibition effectively suppresses the type I interferon response, ultimately leading to increased longevity. Patients with Aicardi-Goutieres syndrome responded significantly less to a type I interferon challenge after receiving low doses of aspirin. Cysteine-containing aspartate proteolytic enzyme one has been shown to inhibit cyclic GMP-AMP (cGAMP) production and the type I interferon response in the wake of DNA virus infection. Specific cleavage of the cyclic GMP-AMP synthase (cGAS) enzyme at the D140 and D157 positions is responsible for this inhibition.[69] Recent studies have shown that protein arginine methyltransferase 5 (PRMT5) can inhibit the manufacture of type I interferons by blocking the binding of cyclic GMP-AMP synthase (cGAS) with DNA. This inhibitory effect on cGAS is achieved through methylation of the R124 residue. The substitution of arginine at the R124 position of cGAS with lysine or PRMT5 inhibitors has decreased cGAS methylation and facilitated a substantial restoration of the suppressed type I interferon response.[70] Gaining a comprehensive understanding of the modification after translation mechanism of cGAS and its associated role would contribute to the enhanced elucidation of the mechanism underlying diseases influenced by the CGAS-STING pathway. The user's text needs to be longer to be rewritten academically. This paper aims to explore the signalling pathways activated downstream of the cGAS-STING pathway and elucidate their respective biological activities.

Innate Immune Pathway Induced by cGAS-STING

Self-DNA leakage from microbes and viruses is a common cause of cytoplasmic DNA release, which is thought to activate STING.[71] Cyclic guanosine monophosphate-adenosine monophosphate is synthesized by the enzyme cyclic GMP-AMP synthase (cGAS) in response to the cytosol's double-stranded DNA (dsDNA). Adenosine triphosphate and guanosine triphosphate are used as fuel in this procedure.[72,73] The secondary messenger cyclic GMP-AMP causes STING to dimerize and activate. TANK-binding kinase 1 (TBK1), linked to the TRAF group member-related NF-kappaB activator (TANK), is then recruited. Interferon regulatory factor 3 phosphorylation is facilitated by TBK1, which acts as a molecular scaffold.[40] At the same time, TBK1 aids in importing nuclear factors kappa B (NF-B). Type I interferon and additional transcription outputs, like tumour necrosis factor-alpha (TNF-) and interleukin-6 (IL-6), are significantly expressed towards the end of this chain of events, amplifying the inflammatory reaction.[74]

To a large extent, IFN-I production is controlled by the cGAS-STING pathway. Several inflammatory diseases, collectively called

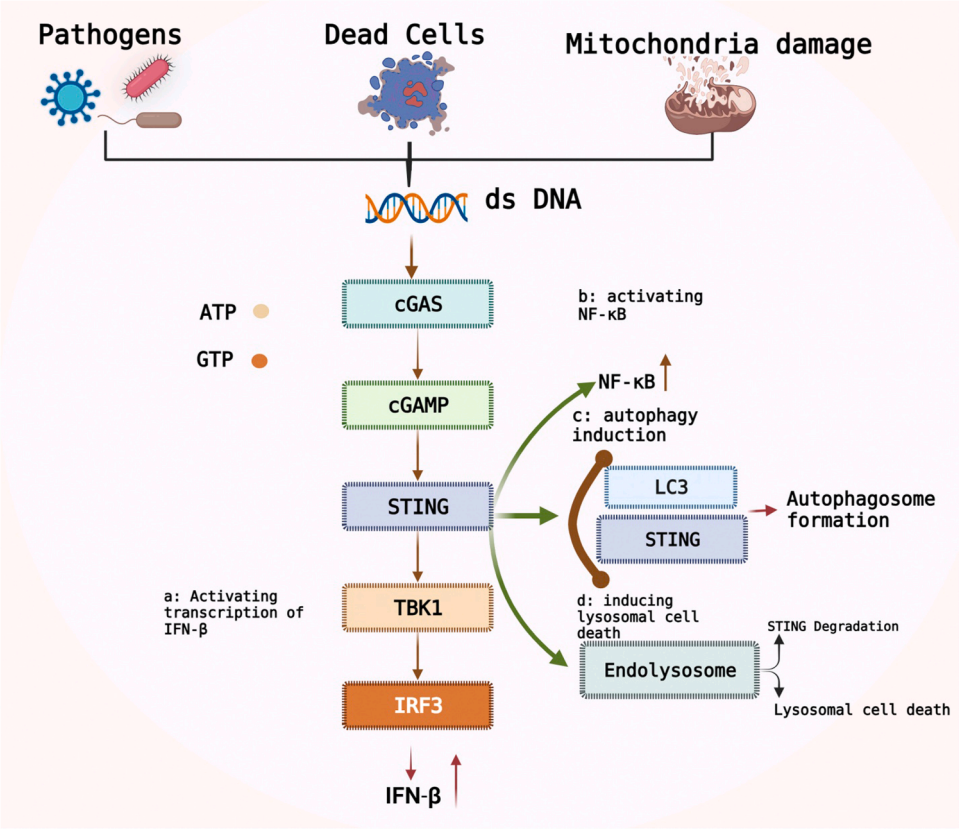

Fig. 2. Biological roles of the cGAS-STING signalling pathways. a: The DNA-binding activation of cGAS generates 2′,3′-cGAMP, which triggers the transcription factor STING. This causes IRF3 to become phosphorylated and express IFN-, activating TBK1. b: STING-dependent activation of NF-kappaB can be mediated by TBK1, although other mechanisms remain to be discovered. c: STING promotes autophagosome production by facilitating LC3 lipidation. d: As soon as STING is activated, it travels to endolysosomes, opening the lysosomal membrane and triggering cell death.

"type-I interferonopathies," can result from abnormally high amounts of IFN-I.[75] In excess amounts, interferon type I (IFN-I) has been related to conditions including systemic lupus erythematosus (SLE). Autoantibody production and inflammatory mediators, including TNF- and IL-1, were significantly reduced in Fcgr2b-null lupus mice, leading to less severe glomerulonephritis. Furthermore, the introduction of bone marrow-derived dendritic cells (BMDCs) that were activated by STING into lupus animals lacking Fcgr2b, in the absence of STING, resulted in the reversal of the previously observed protective effect against the development of lupus. This was demonstrated by elevated amounts of anti-dsDNA antibodies and specific inflammatory characteristics.[76,77]

cGAS-STING-TBK1-IRF3 classical pathways mediates type I

The current investigation reveals that the interaction between cGAS and dsDNA leads to the formation and activation of a dimer of 2. In addition, dsDNA longer than 16 base pairs can bind to sites A and B on the surface of cGAS, leading to the enzyme's activation in both locations at once. Type I interferon expression did not significantly change when THP1 cells were stimulated with 88–4,003 bp dsDNA at a concentration of 1.67 g/mL.[78,79] However, it has been discovered that the ability of double-stranded DNA (dsDNA) to stimulate the expression of type I interferon is strongly related to the length of the dsDNA, even at low DNA concentrations (0.167 and 0.0167 g/mL). This indicates that microbial DNA in the cytoplasm, even at low amounts, can activate the immune system's protective response. Double-stranded DNA (dsDNA) induces a conformational change in the catalytic domain of cyclic GMP-AMP synthase (cGAS), which in turn catalyzes the production of 2′,3′-cGAMP from ATP and GTP in a two-step process. The second messenger function is then provided by cyclic GMP-AMP (cGMP), which binds to the endoplasmic reticulum-localized STING and activates it.[80] After STING has been activated, conformational changes occur, forming a polymer complex. The Golgi apparatus receives this complex after it has been shuttled from the ER.[81–83] The palmitoylation of two cysteine residues (Cys88/91) on STING proteins occurred upon translocation to the Golgi apparatus. Despite the lack of a good understanding of the precise mechanism of palmitoylation, this biological process is essential for activating STING and subsequent molecules.[84] Simultaneously, the protein known as STING will engage in the recruitment and phosphorylation of TBK1 using its C-terminal TANK-binding kinase 1 (TBK1) binding sequence. The activation of TBK1 leads to the subsequent phosphorylation of a conserved consensus motif (pLxIS) situated at the C-terminal region of the neighbouring STING protein. Following this, interferon regulatory factor 3 (IRF3) binding to the phosphorylated pLxIS sequence occurs near TBK1, facilitating the phosphorylation of IRF3 and ultimately encouraging the dimerization of IRF3 within the nucleus.

Consequently, the upregulation of type I interferon expression can be observed (Fig. 2a).[85–87] A crucial immune defence mechanism is the cGAS-STING pathway. Multiple studies, including those looking at the generation of type I interferon reaction in response to DNA virus infections such as Kaposi sarcoma-associated herpes virus and herpes simplex virus type I, support a pivotal role for the cGAS-STING pathway in the immune response to viral infections.[88,89]

cGAS-STING-NF-κB pathways mediates inflammatory response

In addition to the conventional Cgas-Sting-TBK1-IRF3 route, recent research has revealed that the cGAS-STING signalling pathway can exert additional activities via alternative pathways that are not reliant on IRF3. Studies have demonstrated that the cGAS-STING signalling pathways aid in activating NF-kappa B and mitogen-triggered protein kinases, two essential players in the stimulation of the inflammatory response. Although the cGAS-STING regulating pathway is known to activate NF-B and MAPK, the mechanism by which this occurs remains poorly understood. Mitochondrial DNA (mtDNA) release into the cytoplasm has been linked to the nucleoprotein TAR DNA/RNA bind protein 43 (TDP-43).[90,91] The opening of mitochondrial permeation conversion pores is responsible for this release.

The scientists also noted that this process upregulates NF-B and activates the cGAS-STING pathway. In animals with amyotrophic lateral sclerosis (ALS), generated pluripotent stem cells significantly reduced NF-B expression in the brain and spinal cord. In addition, STING inhibitors markedly reduced neurodegeneration in ALS models and mice with motor neurons generated from induced pluripotent stem cells. Furthermore, another research group have reported that the stimulating energy of TBK1 is responsible for the up-regulation of NF-κB expression.[71,92] Nevertheless, the Other study demonstrated that the observed decrease in NF-κB expression was not statistically significant following the deletion mutation of the STING C-terminal in both human and mouse cells.[93–95] In addition, it has been demonstrated that STING can induce the upregulation of NF-κB expression in Drosophila melanogaster via an immunological deficiency pathway that is not reliant on TBK1, as depicted in Fig. 2b.[96] While the exact involvement of TBK1 in STING-mediated NF-κB activation has yet to be investigated, researchers widely acknowledge that the activation of NF-κB is a crucial prerequisite for the full induction of the type I interferon response.[97,98] In cells with non-activated or inhibited NF-κB expression, transfection of dsDNA or viral infection only leads to a limited production of type I interferon.[99,100]

cGAS-STING-LC3 pathways mediates autophagosome formation

The cGAS-STING signalling pathway can have anti-pathogen effects in some pathogen infections, including those caused by mycobacterium tuberculosis, herpes simplex virus, and some gram-positive bacteria, by inducing autophagy in addition to its anti-pathogen effects through the activation of IRF3 and NF-B.[23,101,102]As soon as cGAMP activates it, STING transits through the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) to the Golgi apparatus.[103] The presence of ERGIC, which includes STING, can act as a provider of LC3 lipidization, an essential process in the production of autophagosomes.[104,105] Additionally, cGAMP may also facilitate LC3 lipidization through the utilisation of WIPI2 and ATG5 pathways (Fig. 2**c**). The stimulation of autophagy may still occur in anemones even in the absence of the C-terminal region of STING. This finding suggests that the ability to induce autophagy

might be STING's ancient and fundamental function. Hence, the mechanism by which type I interferon expression is regulated, namely through the involvement of TBK1 and IRF3 in the cGAS-STING signalling pathway, is distinct from the pathway responsible for autophagy induction.[106,107] However, it is noteworthy that these two pathways can synergistically contribute to several biological functions, including combating viral infections and eliciting inflammatory responses.

Comparison of cGAS-STING with other key biological activities

Inflammation

The cGAS-STING pathway's capacity to support innate immunity has been emphasized in numerous studies. For example, streptavidin, a protein released by bacteria, enhances the interaction involving cGAS and DNA, enhance the activation of cGAS and the consequent release of IFN-β.[108] It has also been found that streptavidin nanoparticles and proteins can promote cGAS activation, leading to IRF3 phosphorylation, in research involving cells contaminated with HSV-1 and mice models. The additional investigation unveiled that streptavidin had a role in eliminating herpes simplex virus (HSV) via activating the cGAS-STING-mediated innate immune response. Researchers have created several STING agonists for potential application in cancer immunotherapies, acknowledging the crucial role of STING in immunological defence.[109,110] Additionally, by using this specific pathway, the manufacturing of numerous cytokines and other substances expressed by Interferon-Stimulated Genes, hence boosting the inflammatory response.[111,112]

Activation of the cGAS-STING-IRF3 signalling pathway was associated with an increase in IL-18 and IL-1 levels in mice with obesity-related diabetic cardiomyopathy (DCM). The inflammatory response was made much worse due to this cytokine level increase compared to the control groups. However, the removal of STING reduced the inflammatory response.[113] It was found that TNF-, IL-18, and IL-1 levels were increased in the transverse aortic constriction (TAC) mouse model used to simulate pressure overload-induced heart failure.[114] Furthermore, the study observed that at 1 and 6 weeks following the surgical procedure, the inhibition of cGAS led to a reduction in the levels of these factors and the total recruitment of macrophages, resulting in a similarity to the control group.[49,115] In an experimental animal model simulating myocardial infarction, the M2 macrophages underwent a phenotypic transformation into M1 macrophages by activating the cytosolic DNA-cGAS pathway. The conversion occurred within macrophages that had undergone prior treatment with interferon-stimulatory DNA. This conversion was accompanied by an upregulation in the expression of specific inflammatory mediators, including inducible nitric oxide synthase (iNOS) and C-X-C motif cytokine ligand-10.[116,117]

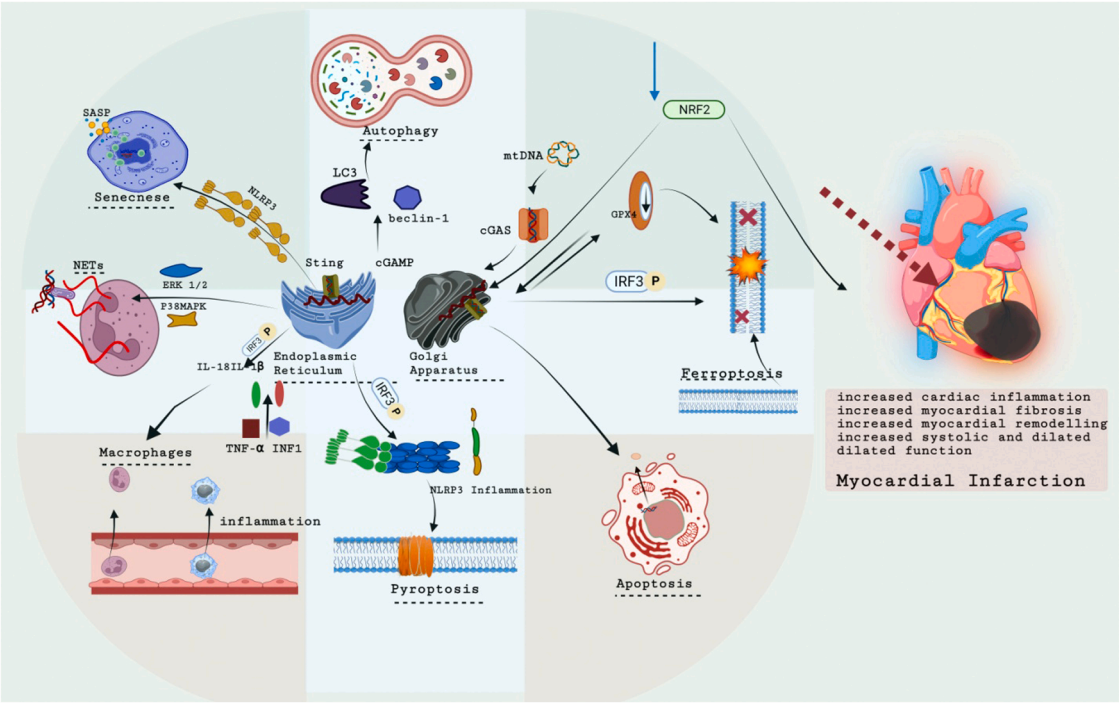

Fig. 3. The interplay of the cGAS-STING pathway with different cellular functions results in myocardial injury. Ultimately, it causes cardiac dysfunction and hypertrophy by inhibiting inflammatory responses, autophagy, ferroptosis, pyroptosis, senescence, NET formation, and apoptosis. [Source: Figure modified from Wan (2023)[48], available at CC BY 4.0].

Neutrophil extracellular traps

The initiation of neutrophil extracellular traps (NETs), which serve as a defensive barrier against microbial invasion, is believed to be prompted by the release of mitochondrial DNA (mtDNA). The liberation of mitochondrial DNA (mtDNA) has the potential to induce a distinct degree of sterile inflammation. The absence of the STING gene regulator in mice resulted in a notable decrease in the activation of neutrophil extracellular traps (NETs) triggered by mitochondrial DNA (mtDNA).[118] Furthermore, neutrophils obtained from the bone marrow of mice that lacked the STING protein exhibited a decrease in neutrophil extracellular traps, even in the presence of mitochondrial DNA stimulation. The findings of this study demonstrate that mitochondrial DNA (mtDNA) can activate neutrophil extracellular traps (NETs) and further elucidate the significant involvement of the stimulator of interferon genes (STING) in this biological process.[119] P38, the mitogen-activated protein kinase, and a kinase regulated by extracellular signal 1/2 are essential in producing this impact.[120]

Cell death

The cGAS-STING pathway is known to initiate the synthesis of INF-I and subsequently induce the expression of inflammation-related proteins, exerting a discernible impact on inflammatory processes and immunity.[121] Recent findings have also shown its crucial involvement in other essential biological processes that impact cellular viability, ageing, or cellular demise at the cellular level (Fig. 3).

Pathogenic effects of cGAS-STING pathway on cardiovascular system

Myocardial infarction

Myocardial ischemia and necrosis, brought on by a lack of oxygen supply or an excess of demand, are the hallmarks of acute myocardial infarction (AMI). After cardiac cell injury and death, damage-associated molecular patterns (DAMPs) are released, activating the innate immune response. Several studies have indicated that the elevation of peripheral blood monocytes following myocardial infarction significantly predicts left ventricular remodelling in patients with this condition. This finding suggests that monocytes may be crucial in the onset and progression of myocardial infarction.[122] In their study, they employed single-cell RNA sequencing analysis to identify and isolate a subset of interferon-inducible cells (IFNICs).[44] These cells were derived from monocytes and found within mice's myocardial infarction area.

Furthermore, immune cell-derived nucleotide-binding oligomerisation domain-like receptors with caspase recruitment domain (NLRP3) inflammasomes (IFNICs) can initiate the cGAS-STING signalling pathway through the process of engulfing foreign DNA. This activation promotes type I interferon production and involvement in ventricular remodelling following myocardial infarction. Conversely, the knockout of cGAS, interferon regulatory factor 3 (IRF3), interferon alpha/beta receptor (IFNAR) genes, or the use of neutralising antibodies against the type I interferon receptor has been shown to alleviate ventricular remodelling in mice effectively. Macrophages can be classified into two distinct phenotypes, M1 and M2, each assuming distinct functional responsibilities. M1 macrophages predominantly exhibit pro-inflammatory and anti-microbial functions, whereas M2 phenotypes primarily assume anti-inflammatory and repair-promoting roles. A study discovered that the suppression of cGAS expression during acute myocardial infarction can induce the conversion of macrophages into the M2 phenotype.[116] After a myocardial infarction, this transformation lessens myocardial damage and speeds up myocardial repair. Therefore, it may be concluded that inhibiting the cGAS-STING signalling pathway's activation in myocardial infarction has therapeutic promise.

Myocardial infarction causes multiple forms of cell harm, including necrosis, apoptosis, and autophagy.[123] The development of holes in the outer membrane of mitochondria occurs during apoptosis due to the activation of Bax (Bcl-2 associated X protein) and BAK (Bcl-2) homologous antagonist/killer). This releases mitochondrial DNA (mtDNA) into the cell's cytoplasm.[124,125] This observation implies that, apart from external DNA, intracellular mitochondrial DNA (mtDNA) might also trigger the cGAS-STING signalling pathway during myocardial infarction. Nevertheless, on the fourth day following the closure of the left coronary artery in mice, it was seen that the red-labelled cells in the infarction area, which were non-responsive to interferon, had the characteristic morphology of cardiomyocytes with myotome. In contrast, the green fluorescent-labeled cells that were responsive to interferon were found to be non-cardiomyocytes.[126] Hence, it is imperative to conduct experimental investigations to ascertain the potential activation of the cGAS-STING signalling pathway and its involvement in the progression of cardiomyocyte injury, specifically in the release of mtDNA into cells.

Heart failure

Heart failure is a syndrome characterised by dyspnea, oedema, and weakness in the lower limbs, as well as symptoms including elevated jugular vein strain, pulmonary oedema, and peripheral oedema.[127] It is brought on by faulty heart structure or function. This factor has been identified as a significant contributor to the rising global mortality rates.[128] The triggering of inflammatory pathways has been linked to the development of left ventricular remodelling and dysfunction in patients with heart failure, supporting the growing body of evidence suggesting heart failure is a persistent inflammatory disease. However, how exactly inflammation plays a role in the development of heart failure is still poorly understood.

Furthermore, it has been seen in clinical trials such as RENEWAL[129], EXACT-HF [130] and OPT-CHF [131] that there needs to be more

discernible impact when employing anti-inflammatory medicine in the treatment of heart failure patients. As a result, studies have been performed to understand better how other inflammatory pathways contribute to heart failure. With any luck, the results of this investigation will add to the growing body of research aimed at identifying novel targets for the treatment and prevention of heart failure.[132,133] Previous research has demonstrated that the use of a left ventricular assist device (LVAD) in patients with heart failure caused by ischemic heart disease results in a decrease in the production of the chemokine CXCL10 and the enzyme responsible for its production, cyclic GMP-AMP synthase (cGAS). This finding is in keeping with previous reports that heart failure is associated with a strong engagement of the CGAS-STING signalling pathway. In a mouse model of heart failure caused by pressure overload, It was found that inhibiting the cGAS-STING signalling pathway reduced inflammation-related variables and inflammatory cell infiltration.[49] This inhibition also reduced apoptosis in cardiomyocytes, which benefited myocardial remodelling and safeguarded heart function. Heart failure and the cGAS-STING signalling pathway have recently begun to be the subject of scientific investigation. Targeting the cGAS-STING signalling pathway may be beneficial for treating heart failure, but further research is needed to determine its exact involvement in the disease's progression.

Myocarditis

Myocarditis has many potential origins, including infectious agents, viruses, bacteria, fungi, parasites, and non-infectious factors such as autoimmune myocarditis and drug side effects.[134] Viral infection plays a role in both the development and progression of myocarditis by causing inflammation, ultimately leading to the necrosis or apoptosis of cardiac cells. Many are riding on this correct pathophysiological process.[135,136] cGAS-STING signalling has been shown to have a double role in viral myocarditis in recent research. In the aftermath of a virus infection, the presence of viral DNA in the cytoplasm has been related to two divergent consequences. It helps the body fight against viruses by stimulating the production of type I interferon via the cGAS-STING signalling pathway. Myocardial damage is exacerbated by inflammation, which can be triggered by activating the cGAS-STING signalling pathway.[137,138]

Furthermore, aside from its involvement in viral myocarditis, cGAS has significant relevance in microbial infections and non-infectious myocarditis. Lipopolysaccharide-induced myocardial injury with sepsis was investigated in an experimental study utilising a mouse model. The study observed a noteworthy elevation in the expression levels of STING and p-IRF3. Furthermore, it was found that the knockout of the STING gene effectively suppressed the inflammatory response, apoptosis, and scarring of cardiomyocytes induced by lipopolysaccharide. This intervention also led to an improvement in cardiac function and an extension of the survival time in mice.[43] Myocarditis can occur after a Trypanosoma cruzi infection because the polyADP ribose polymerase 1-cGAS-NF-B pathway is activated, allowing inflammatory macrophages to be more easily converted. However, this inflammatory response can be dampened by blocking cGAS activation.[139]

It's also important to note that cGAS plays a significant role in determining whether or not autoimmune myocarditis develops. Interferon-beta (IFN-), interferon boosting genes, and cyclic GMP-AMP (cGAMP) levels were successfully reduced in the cardiac tissue of experimental mice with autoimmune myocarditis produced by the knockout of the TREX1 gene by administering medicines that target the blocking of cyclic GMP-AMP synthase. In addition, this therapy has been shown to reduce endocardial fibrosis and inflammation.[140] The pathogenesis, development, and prognosis of myocarditis include the cGAS-STING signalling system. Additional research is required to investigate strategies for mitigating the excessive inflammatory response and subsequent myocardial damage associated with the cGAS-STING signalling pathway while still assuring its anti-pathogenic efficacy.

Cardiovascular disease-related risk factors mediate the cGAS-STING signaling pathway

Through modulating the cGAS-STING signalling pathway, cardiovascular risk factors like ageing, smoking, and obesity also encourage the recurrence and progression of cardiovascular illnesses. Cellular senescence is a condition in which cells halt their normal cell cycle progression due to many circumstances. Senescent cells can secrete diverse inflammatory factors, commonly known as the senescence-associated secretory phenotype (SASP). SASP cells are responsible for the secretion of several autocrine and paracrine substances, which contribute to developing atherosclerosis, intima thickening, endothelial dysfunction, cardiovascular remodelling, arrhythmia, heart failure, and other cardiovascular disorders.[141] The synthesis of the senescence-associated secretory phenotype (SASP) factor can be regulated by oxidative stress, radiation, oncogene activation, and medicines through the cGAS-STING signalling pathway.[142,143] These factors can also induce cell senescence and further regulate the production of the SASP factor. One of the primary forms of free fatty acids, palmitic acid, has the potential to induce mitochondrial damage, release mitochondrial DNA (mtDNA), and then trigger the MTDNa-CgasSting-IRF3 pathway, leading to endothelial cell inflammation and insulin resistance. However, this reaction is notably attenuated in STINGgt/gt mice.[144] Through the genotyping of participants in PolSenior, a comprehensive project conducted across multiple centres and disciplines to evaluate the health and socio-economic conditions of individuals aged 65 years or older in Poland, it was determined that individuals who were obese or smokers and possessed the STING 293Q allele mutation exhibited a reduced likelihood of developing cardiovascular diseases. This finding provides evidence of a significant association between STING and age-related ailments, particularly cardiovascular diseases.[145,146]

Additional evidence is that mitochondrial DNA is released into the cytoplasm upon introducing bacterial endotoxin lipopolysaccharide.[147] This release then phosphorylates YES-related protein 1, which inhibits vascular endothelial cell proliferation via the CGAS-STING signalling pathway. Additionally, the researchers observed that mice's vascular endothelial regeneration capacity with a cGAS gene knockout was notably enhanced. Numerous clinical studies have demonstrated a notable elevation in the likelihood of cardiovascular events among individuals diagnosed with Alzheimer's. In mice carrying the APPswe/PS1dE9 mutation, it has been observed that melatonin can effectively modulate mitochondrial autophagy through the cGAS-STING-TBK1 pathway, facilitated

through ALDH2. This regulatory mechanism contributes to the amelioration of mitochondrial damage and enhancement of cardiac function.[22] The studies above collectively indicate that cGAS assumes a significant role in cardiovascular disease, potentially influencing the onset and progression of such conditions through several pathways.

Supportive data for cGAS-STING's role in cardiovascular disease

The present discourse elucidates how self-DNA activates the cGAS-STING pathway, impacting immune-related ailments and non-immune disorders such as cardiovascular disease (CVD). Upon thorough analysis of the existing body of information, we have identified noteworthy correlations between risk factors associated with cardiovascular disease (CVD) and the cGAS-STING pathway.

To begin with, a correlation exists between the activation of cGAS-STING and smoking, encompassing both direct inhalation and indirect exposure to tobacco smoke.[148] According to existing research, it has been found that exposure to side-stream smoke might result in negative cardiac consequences in mice models.[149] These consequences include decreased fractional shortening (FS) and increased left ventricular (LV) mass. Moreover, the impact of this phenomenon is intensified when there is a hindrance in the process of autophagy, indicating a potential association between the activation of the cGAS-STING pathway and the occurrence of inflammation resulting from smoking. Second, activating the cGAS-STING pathway has also been associated with obesity, a major CVD risk factor.[150] *In vitro* investigations have demonstrated that heightened concentrations of palmitic acid (PA) in the circulatory system, frequently observed in patients with obesity, can elicit mitochondrial impairment and the liberation of mitochondrial DNA (mtDNA) into the cytosol.[144,151] Consequently, the cGAS-STING pathway is triggered, leading to the synthesis of interferons (IFNs).[152]

The process of DNA degradation throughout the ageing process has the potential to contribute to the inflammatory response, potentially through the activation of cGAS-STING.[153,154] In addition to traditional risk factors, cardiovascular diseases (CVDs) such as heart failure[49,155], stroke[156], myocardial infarction[48], infections[157], and radiation injury [158] have been found to exhibit participation in the cGAS-STING pathway. The complex interrelationship highlighted here emphasizes the potential importance of the cGAS-STING pathway in comprehending and mitigating cardiovascular well-being and pathology as shown in Fig. 4.

Conclusions and perspectives

This review investigates the connection between cardiac dysfunction and the cGAS-STING pathway, which is implicated in cell death through multiple physiological functions. The cGAS-STING signalling pathway can impact the onset and progression of cardiovascular disorders, including myocardial infarction, heart failure, and myocarditis, through diverse mechanisms such as

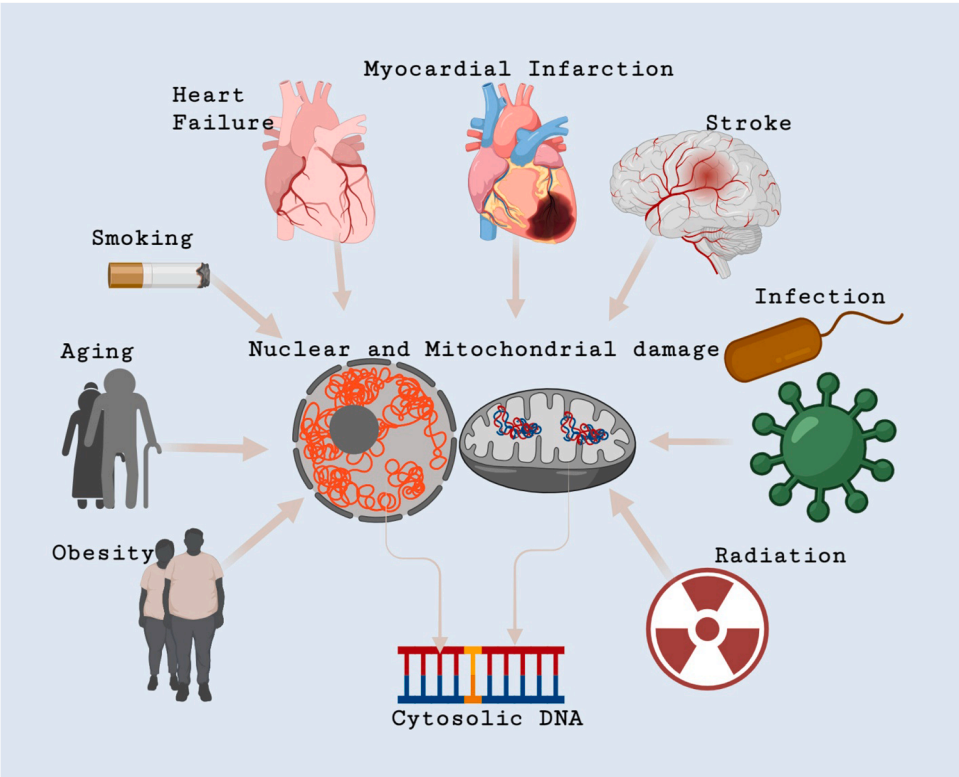

Fig. 4. Cardiovascular diseases (CVDs) and the risk factors linked to the detection of cytosolic DNA. [Source: Figure modified from (2021)[7], available at CC BY 4.0].

inflammation mediation, immune regulation, autophagy promotion, and ageing promotion. Animal experimental studies have confirmed that inhibiting the cGAS-STING signalling pathway yields notable improvements in cardiac function across various cardiovascular diseases, including myocardial infarction, heart failure, myocarditis, and related conditions. Additionally, this inhibition has been observed to extend the survival of experimental animals. As a result of these results, the cGAS-STING signalling pathway has been proposed as a promising therapeutic target for cardiovascular disorders. However, there are numerous cardiovascular diseases, each with its unique causes. We need to expand and clarify our knowledge of the CGAS-STING signalling pathway and its role in various cardiovascular diseases. An instance of promoting angiogenesis can be observed by suppressing cGAS expression after myocardial infarction.

Recent years have seen a renaissance in microbiome science, specifically in studying bacteria and their DNA concerning cardiovascular diseases (CVDs) and metabolic disorders. Significant relationships have been found between microbial DNA and important metabolic traits such as platelet activation, vascular and metabolic inflammatory processes, glucose and lipid metabolism, obesity, and insulin sensitivity.Increased quantities of microbial DNA have been detected in plaque locations inpatient cases of atherosclerotic CVD. It has been challenging to show a causal relationship between abnormal pathology and intracellular signalling processes. It is also important to note that microbial DNA from dangerous and helpful bacteria living in body cavities can activate the STING signalling pathway.

In addition, it has been discovered that STING pathway activation disrupts the intestinal barrier in the gut, leading to increased bacterial translocation and inflammation in the intestines. This begs the question of whether or not STING signalling contributes to the pathogenic metabolic alterations in the vasculature caused by microbial DNA. STING's intestinal barrier breakdown also increases the translocation of pathogenic bacteria byproducts like LPS and the escape of commensal bacteria. In turn, these waste products trigger TLR to eliminate inflammation. Future studies should investigate the respective contributions and potential synergistic interactions of other double-stranded DNA-sensing pathways and STING signalling to understand the function of dsDNA-sensing signalling cascades in vascular biological processes and systemic inflammation. Pharmacological inhibitors engaging cGAS and STING in the setting of CVDs and metabolic illnesses are primarily unexplored, with genetic modification techniques being the primary treatment modality. However, it is becoming increasingly apparent that focusing on the cGAS-STING pathway has excellent potential for treating prevalent sterile inflammatory ailments like cardiovascular diseases and metabolic disorders. Therefore, cGAS and STING pharmacological antagonists are practical treatment methods in the ongoing fight against cardiovascular disease and metabolic disorders. The mystery of STING's function in cardiovascular and metabolic disorders will be solved as continuing research efforts progress.

Concluding remarks

In conclusion, persistent low-grade sterile inflammation, associated with metabolic problems and cardiovascular illnesses, is strongly linked to the cGAS-STING innate immune signalling system. Most notably, it is a pivotal link between the immune and metabolic systems. The current research findings are encouraging, but many unanswered questions remain. These include the need to understand the tissue-specific interactions between this pathway and metabolic processes, investigate the epigenetic effects of the cGAS-STING pathway in the context of CVDs and metabolic diseases, outline the functions of STING and cGAS about the cardiovascular and metabolic mechanisms, and gather more proof that STING-induced chronic inflammation occurs in people with CVDs and metabolic disorders.

The findings highlighted in this review provide interesting new directions for future translational research projects focusing on CVDs and metabolic diseases despite the limits of the existing database. These studies will help us better understand the complex role of the cGAS-STING pathway in various diseases.

Author contributions

MSK, SK, MS and MUK writing original paper. MSK collecting data of articles. RA,IK and MIK drawing diagrams. SK supervision, project administration and funding acquisition. All authors contributed to the article and approved the submitted version.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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