Review

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Review

The cGAS/STING Pathway: Friend or Foe in Regulating Cardiomyopathy

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Abstract: Inflammation is a key hallmark in cardiomyopathy where misdirected immune activation causes chronic myocardial dysfunction. Among the emerging mechanisms implicated in the dysfunction, the cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING) signaling pathway has attracted significant attention. Acting as a critical DNA sensor, the cGAS/STING pathway coordinates inflammatory responses triggered by microbial invasions or endogenous stressors such as autophagic or apoptotic cell death. Despite its pivotal role, the precise molecular mechanisms regulating this pathway and its contribution to aberrant inflammation in cardiomyopathy remain poorly understood and controversial. To address this scientific gap, we first summarized the key findings on the cGAS/STING pathway in different cardiomyopathies using in vivo/in vitro models as well as clinical samples. In the next step, we explored how the cGAS/STING pathway could be modulated by it agonists and antagonists in cardiomyopathy. Finally, leveraging publicly available human single-cell ribonucleic acid sequencing (RNA-seq) dataset and systematic literature review, we identified existing molecular interventions and highlighted potential therapeutic targets to mitigate cGAS/STING-driven inflammation. This integrative approach underscores the therapeutic potential of targeting the cGAS/STING pathway and provides a foundation for developing novel interventions aimed at alleviating inflammatory cardiomyopathy and improving patient outcomes. Future studies will be crucial in validating these findings and translating them into clinics.

Keywords: cardiomyopathy; cGAS/STING pathway; mitochondria; DNA damage

1. Introduction

Cardiomyopathy is a type of cardiac disease in which the heart muscle is structurally and functionally altered [1]. Cardiomyopathies can be divided into dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and unclassified cardiomyopathies [2,3]. Patients with cardiomyopathies may experience a range of symptoms, varying with the type and severity of the condition. Common manifestations include dyspnea, fatigue, chest pain, arrhythmia and even sudden cardiac death [1]. Current treatment for cardiomyopathy mainly focuses on managing the symptoms and preventing

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complications. To date, no specific drug has been approved for the causal treatment of cardiomyopathies [4]. Therefore, it is crucial to understand the underlying mechanism to identify novel therapeutic targets for the disease.

Many studies have investigated signaling pathways in different cardiomyopathy models and found that several cellular and metabolic pathways, which include β-adrenergic signaling, MAPK/ERK signaling, WNT signaling, Hippo-Yes-associated protein signaling, CaM-kinase signaling, and autophagy signaling, are altered [5–8]. Recently, there has been extensive research into the cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase/stimulator of interferon genes (cGAS/STING) pathway, highlighting its function in sensing cytosolic DNA and triggering downstream inflammation and cell death [9–12]. However, the role of the cGAS/STING pathway in cardiomyopathy and its regulatory mechanisms are not yet fully understood. This review seeks to provide comprehensive knowledge about molecular intervention targeting the cGAS/STING pathway in cardiomyopathy.

2. Overview of the cGAS/STING Signaling Pathway

The cGAS/STING pathway is a crucial element of the innate immune response which detects the presence of cytoplasmic DNA and subsequently triggers the expression of inflammatory genes. Cytosolic DNA can originate from both exogenous and endogenous sources [13]. Viruses and bacteria can be sources of exogenous DNA, while endogenous DNA mainly originates from cell apoptosis, auto cellular death, and mitochondrial damage. As shown in ***Figure 1***, The main components of this pathway include cyclic GMP-AMP synthase (cGAS), cyclic GMP-AMP (cGAMP), stimulator of interferon genes (STING), TANK-binding Kinase 1 (TBK1), interferon regulatory factor 3 (IRF3), Type I Interferons (e.g., IFN-β), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). cGAS exists ubiquitously in the cytoplasm as a so-called DNA sensor [14]. Upon binding to double-stranded DNA (dsDNA), it undergoes conformational change and catalyzes the production of cGAMP from ATP and GTP. cGAMP then acts as a second messenger and activates STING. The activation of STING mediates its translocation from the endoplasmic reticulum membrane to the endoplasmic reticulum-Golgi intermediate compartment and Golgi apparatus, phosphorylating TBK1. Phosphorylated TBK1 then phosphorylates and activates IRF3, which serves as a transcription factor. Phosphorylated IRF3 moves into the cell nucleus and triggers the expression of type I interferons [15,16]. Simultaneously, STING activation also triggers NF-κB activation, which subsequently enhances the expression of pro-inflammatory cytokines.

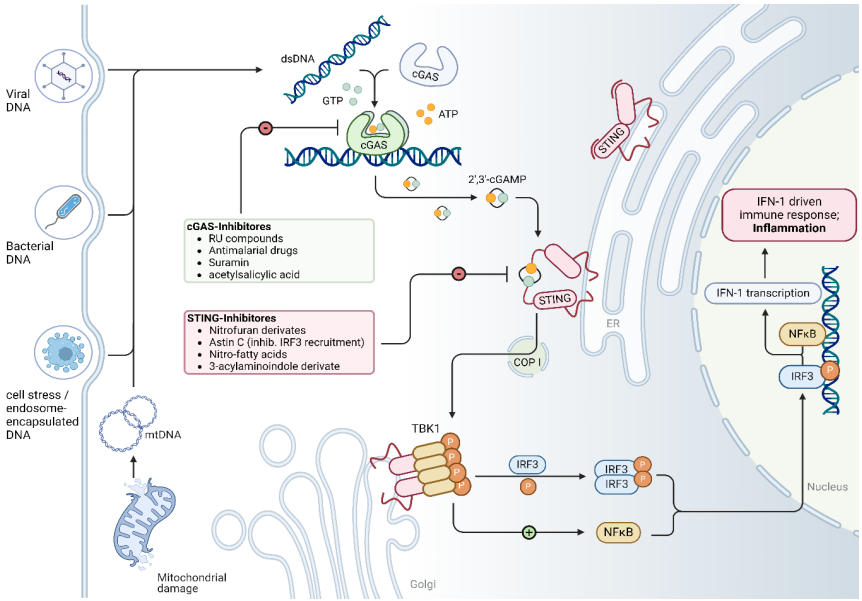

Figure 1. Schematic illustration of the cGAS/STING pathway. Cyclic guanosine monophosphate adenosine monophosphate synthase (cGAS), which is freely present in the cytosol, binds to both exogenous and

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endogenous double-stranded DNA (dsDNA). Viruses and bacteria can be sources of exogenous dsDNA, while endogenous dsDNA mainly originates from cell apoptosis, auto cellular death as well as mitochondrial damage. After binding to dsDNA, cGAS catalyzes a reaction between ATP and GTP to form 2′,3′-cGAMP. 2′,3′-cGAMP then binds to the 'stimulator of interferon genes' (STING), located on the membrane of the endoplasmic reticulum (ER), triggers a conformational change and subsequently activates STING. The activated STING is transported to the Golgi apparatus via the coatomer protein complex I (COP I), where it phosphorylates TANK-binding kinase 1 (TBK1) to form a tetramer. TBK1 then phosphorylates interferon regulatory factor 3 (IRF3), which dimerizes and enters the nucleus together with nuclear factor kappa B (NFκB) to induce the expression of type 1 interferons as well as other proinflammatory cytokines. Many chemical compounds are known to modulate the cGAS/STING signaling pathway (see green and red box).

3. Activation of cGAS/STING Pathway in Different Cardiomyopathies

Inflammation is a key factor in the development and progression of a variety of cardiomyopathies [17–20]. Recent evidence suggests that cGAS/STING-mediated inflammation and apoptosis are involved in myocardial damage and remodeling, which might contribute to the development of cardiomyopathy [21–23]. To better demonstrate the essential function of cGAS/STING-signaling in inflammation-mediated cardiomyopathies, we first systematically review the most important studies of the cGAS/STING signaling pathway in various types of cardiomyopathies (see ***Table 1***).

Table 1. Main studies on cGAS/STING pathway in cardiomyopathy.

Cardiomyopathy	Year	Model	Methods	Conclusion	Ref
Sepsis-induced cardiomyopathy (SIC)	2019	· In vivo: Male mouse injected with LPS · In vitro: Neonatal rat cardiomyocytes (NRCMs); H9C2 cells	· IB · IF · Real time RT-qPCR	· cGAS/STING is activated in LPS-treated heart tissues and cardiomyocytes. · Activated molecules: NLRP3, IRF3, IL-1β, TNF-α, MCP-1, HMGBA, caspase-1, IL-18 · STING knockdown inhibits LPS-induced phosphorylation and nuclear translocation of IRF3, suppresses inflammation, apoptosis and pyroptosis, improves cardiac function and survival.	[1]
	2022	· Human blood samples · In vivo: Male mouse injected with LPS · In vitro: RAW 264.7 macrophages. H9C2 myofibroblasts	· IB · IF/IHC · Real time RT-qPCR	· STING is activated in LPS-treated cardiac tissues. · STING is increased in the peripheral blood samples of septic patients. · Activated molecules: TNF-α, IL-1β, IL-6, COX2. · ICA69 knockout inhibits STING-mediated inflammation and ferroptosis.	[2]

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	2023	· In vivo: LPS-treated mouse · In vitro: LPS-stimulated H9C2 cells (rat cardiomyocytes)	· IB · ELISA · IF/IHC	· cGAS/STING is activated in both heart tissue and H9C2 cells following LPS treatment. · Activated molecules: IRF3, TBK1, IL-6, IL-1β, TNF-α. · Knocking down cGAS in H9C2 cardiomyocytes alleviates cardiac inflammation and apoptosis induced by LPS. · ALDH2 inhibits cGAS/STING signaling both in vivo and in vitro.	[3]
Dilated cardiomyopathy	2023	· In vivo: Myh6-Cre:LmnaF/F:Crat-/- mouse · In vitro: Neonatal rat ventricular myocytes (NRVMs)	· IB · IF/IHC · Real time RT-qPCR · RNA-Seq · scRNA-Seq	· cGAS and type I interferon responses are activated in CRAT-deficient NRVMs. · Activated molecules: IL-1β, IL-6, TNF-α · Knockdown of cGAS abrogates interferon-stimulated gene expression.	[4]
	2023	· Human hearts with DCM	· IB · RNA-Seq	· cGAS is increased in human heart samples from patients with primary DCM. · STING1 and phospho-STING1 (serine residue 365) are unchanged. · Activated molecules: TBK1.	[5]
	2022	· In vivo (LMNA–DCM model): Myh6-Cre:LmnaF/F mouse; Myh6-Cre:LmnaF/F:Mb21d1-/- mouse	· IB · IF	· cGAS/STING is activated in LMNA-DCM whole heart tissue. · Activated molecules: ATM, H2AFX, p-TP53, total TP53, CDKN1A. · Knockout of CGAS prolonged survival, improved cardiac function, partially restored levels of molecular markers of heart failure, and attenuated myocardial apoptosis and fibrosis in the LMNA-deficient mice.	[6]
	2024	· In vivo (LMNA–DCM model):	· IF/IHC · snRNA-seq	· cGAS/STING-related transcription is not activated in cardiomyocytes.	[7]

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		LmnaF/F;Myh6-MerCreMer mouse		· CGAS or STING knockout does not rescue the phenotypes of LMNA-DCM.	
Diabetic cardiomyopathy	2022	· In vivo: Male db/db and db/+ mouse · In vitro: Palmitic acid (PA)-treated H9C2 cells (rat cardiomyocytes)	· IB · IF/IHC · Real time RT-qPCR	· Mitochondria-derived mtDNA can activate cGAS/STING pathway in cardiomyocytes. · Activated molecules: IRF3, NF-κB, IL-18, IL-1β. · Knockdown of STING in H9C2 cardiomyocytes and inhibition of STING with C176 can ameliorate myocardial inflammation and apoptosis.	[8]
	2022	· In vivo: Male mouse · In vitro: Palmitic acid (PA)-treated H9C2 cells (rat cardiomyocytes)	· IB · IF/IHC · Real time RT-qPCR	· Cytosolic mtDNA activates cGAS/STING in DCM hearts and H9C2 cells. · Activated molecules: p-TBK1, p-IRF3, NLRP3, caspase-1, GSDMD, TNF-α, INF-β, IL-1β, IL-18. · cGAS or STING knockdown inhibits cardiomyocyte pyroptosis and inflammation.	[9]
	2023	· In vivo: STZ-treated mouse; db/db mouse · In vitro: Neonatal rat cardiomyocytes (NRCMs); cultured cardiac fibroblasts; endothelial cells	· IB · IF · TUNEL · Real time RT-qPCR	· cGAS/STING is activated by ULK1 in cardiomyocytes. · Metrnl downregulation exacerbates high glucose-elicited hypertrophy, apoptosis, and oxidative damage in neonatal rat cardiomyocytes. · Metrnl activates the autophagy pathway and inhibits the cGAS/STING signaling in a LKB1/AMPK/ULK1-dependent mechanism in cardiomyocytes.	[10]
	2023	· In vivo: STZ-treated and HFD-fed mouse · In vitro: Neonatal rat cardiomyocytes (NRCMs)	· IB · IF/IHC · Real time RT-qPCR · TUNEL	· cGAS/STING is activated in cardiomyocytes both in vivo and in vitro. · Activated molecules: p-TBK, p-NF-κB, IL-1β, Caspase-3. · BRG1 deficiency results in the accumulation of dsDNA and triggers cGAS/STING, exacerbating cardiomyocyte	[11]

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				inflammation and apoptosis induced by hyperglycemia and hyperlipidemia.	
	2024	· In vivo: Human blood samples; STZ-treated and HFD-fed mouse · In vitro:	· IB · IF/IHC · Real time RT-qPCR · TUNEL	· cGAS/STING is activated in fibroblasts which engulf released extracellular vesicles containing mtDNA from cardiomyocytes. · Activated molecules: p-TBK1, p-IRF3, p-p65, IL-37. · IL-37 ameliorates mitochondrial injury, reduces the release of mtDNA-enriched vesicles, which attenuates the progression of DCM.	[12]
	2024	· In vivo: STZ-treated and HFD-fed mouse · In vitro: HG/HF-treated H9C2 cells	· IB · IF/IHC · Real time RT-qPCR	· cGAS/STING is activated in myocardium and H9C2 cells. · Activated molecules: MITOL, NLRP3, Caspase 1, IL-1β, GSDMD. · Irisin and MITOL administration alleviates cardiac dysfunction via inhibition of the cGAS/STING pathway.	[13]
Other cardiomyopathies	2021	TMEM43 arrhythmogenic cardiomyopathy · In vivo: Myh6-Cre:Tmem43W/F mice	· IB · IF · bulk RNA-Seq	· cGAS/STING is activated in cardiomyocytes at later stage. · Activated molecules: pATM, ATM, pH2AFX, LGALS3, VCAN, GDF15, TGFβ1.	[14]
	2020	Chagas cardiomyopathy · In vivo: *T. cruzi* trypomastigotes infected mice · In vitro: Murine bone marrow cells; RAW 264.7 macrophages; C2C12 mouse myoblast cells	· IHC · Real time RT-qPCR	· cGAS/STING is the early responder in recognizing T.cruzi-induced extracellular vesicles stimulus and signaling proinflammatory cytokine gene expression in macrophages. · Activated molecules: NF-κB, IL-6, IL-1β, TNF-α. · PARP1 synergizes with cGAS in signaling the NF-κB transcriptional activity in macrophages; inhibition of PARP1 reduces myocardial inflammatory infiltrates and	[15]

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				improves the left ventricular function.	
	2024	Stress cardiomyopathy · In vivo: Ovariectomized mice treated with isoproterenol; · In vitro: RAW 264.7 macrophages	· IF/IHC · bulk RNA-seq	· STING is activated in macrophages. · Activated molecules: TBK1, TNF, IL6, CCL2, IFN-β. · Ginsenoside Rb1 suppresses DNA-stimulated STING-mediated proinflammatory activation of macrophages.	[16]
	2023	LEMD2 arrhythmogenic cardiomyopathy · In vivo: Lemd2 p.L13R knock-in mouse · In vitro: HeLa LEMD2 p.L13R KI; HeLa LEMD2 DEL; HEK293	· IF · bulk RNA-seq	· cGAS is recruited to the nuclear envelope rupture sites and micronuclei, subsequently activating cGAS/STING/IFN pathway in mutant LEMD2 cell lines. · Activated molecules: H2AFX, SASPs (Gdf15, Tgfβ2 and Edn3)	[17]
	2023	Doxorubicin-induced cardiomyopathy · In vivo: Male mouse treated with doxorubicin for acute injury	· IB · IF/IHC · Real time RT-qPCR · TUNEL	· cGAS/STING is activated in myocardium. · Activated molecules: p-IRF3, p-p65, p-TBK1. · STING knockdown reduces vacuolization and myofibril loss, suppresses inflammation and apoptosis, improves survival and cardiac function.	[18]
	2023	Doxorubicin-induced cardiomyopathy · In vivo: Mouse treated with low-dose doxorubicin for chronic injury · In vitro: human cardiac microvascular endothelial cells (HCMECs)	· IB · IF · Real time RT-qPCR · bulk RNA-Seq	· cGAS/STING is activated in cardiac endothelial cells. · Activated molecules: p-TBK1, p-IRF3 · Global cGAS, Sting, and Irf3 deficiency ameliorates DIC. · Endothelial cell-specific Sting deficiency prevents DIC and endothelial dysfunction.	[19]

3.1. Dilated Cardiomyopathy

Dilated cardiomyopathy is marked by enlargement and impaired contraction of one or both ventricles. It is a leading cause for heart failure and a primary indication for heart transplantation [24–26]. Up to 40% of all dilated cardiomyopathies in humans are of genetic origin, with most mutations affecting genes coding for cytoskeletal or contractile proteins [27,28]. The following systematically reviews some of the most common mutations and the corresponding animal models.

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3.1.1. LMNA Cardiomyopathy

Mutations in the LMNA gene, which encodes for the nuclear envelope proteins lamin A and C, represent the second most common genetic cause of DCM [29,30]. Lamin A/C are components of the nuclear lamina, providing structural support to the nucleus and serving as a platform for protein interactions involved in gene regulation, DNA replication, and genome stability [31–34]. Disruption in lamin A/C can result in abnormal nuclear shape, impaired DNA repair, and altered gene expression [35–38].

In 2022, Cheedipudi et al. reported on the activation of the DNA damage response pathway in LMNA-deficient mice and found that genetic blockade of cGAS in these mice increased survival, improved cardiac function, reduced cardiac fibrosis and apoptosis39. In mice with LMNA cardiomyopathy, multiple components of the cGAS/STING pathway as well as its downstream targets, including cGAS, TBK1, STING1, pIRF3, and NF-kB, showed marked upregulation in the heart. Genetic knockout of cGAS in these mice significantly reduced the levels of all these components except for STING1 [39]. However, in 2024, En et al. challenged these findings and proposed that cGAS/STING does not contribute to lamin A/C-dependent cardiomyopathy in adult mice. They found that the phenotypes of adult *Lmna*-deficient mice could not be rescued by either cGAS or STING knockout [40]. They showed that cGAS/STING was not activated in cardiomyocytes and attributed this to the generally low expression levels of cGAS and STING in adult cardiac myocytes. Instead, after enriching the upregulated genes in the hearts of LMNA cardiomyopathy mice from single-nucleus RNA-seq data, they proposed that extracellular matrix signaling is activated instead and acts as a potential inflammatory mediator [40]. More recently, Zuela-Sopilniak et al. conducted a multi-level transcriptomic analysis of LMNA DCM and characterized two subclusters of cardiomyocytes responsible for the DCM pathogenesis [41]. Within these subclusters, despite the low transcriptional expression level of cGAS, STING was found to be activated, possibly due to another cytoplasmic DNA sensor: Gamma-interferon-inducible protein 16 (IFI16). Interestingly, they hypothesized that the activation of cGAS-independent cytosolic pattern recognition pathways and DNA damage response pathways in cardiomyocytes subsequently triggered transcriptomic changes in cardiac fibroblasts, the recruitment of immune cells and activation of extracellular matrix remodeling, which eventually led to cardiac dysfunction [41].

Several reasons could possibly explain these contrary findings. Firstly, the LMNA DCM animal models utilized by these research groups differed. Cheedipudi et al. used *Myh6-Cre:Lmna*$^{F/F}$ mice in which LMNA was deleted postnatally, while En et al. used inducible Cre recombinase to delete LMNA in cardiomyocytes at 6-8 weeks of age [40]. The activated pathways may vary depending on the timing of LMNA knockout, especially as different pathways undergo changes during cardiac development. It remains uncertain which approach more accurately replicates human LMNA cardiomyopathy. Secondly, the methods used to assess cGAS/STING activity differ between the two studies. Cheedipudi et al. employed immunoblot analysis to assess the expression levels of key proteins involved in the cGAS/STING pathway, while En et al. investigated the activity of key genes from this pathway at the transcriptional level. Evidence showed that mRNA and protein levels often show a weak correlation, likely due to post-transcriptional regulation and post-translational modifications. As a result, transcript abundance may not reliably reflect cGAS/STING signaling activity, which could explain the discrepancies between the findings of En et al. and Zuela-Sopilniak et al. compared to those of Cheedipudi et al. [39–41].

3.1.2. LEMD2-Associated Cardiomyopathy

Similar to lamin A/C, the LEM domain-containing protein 2 (LEMD2) is a critical component of the nuclear membrane which maintains nuclear structure [42,43]. Mutations in the LEMD2 gene, specifically the c.T38>G (p.L13>R) mutation in humans, cause dilated cardiomyopathy with arrhythmic features [44–46].

In 2022, Caravia et al. generated the first LEMD2-associated cardiomyopathy mouse model to investigate the role of LEMD2 in cardiac development and heart disease. They found that both the

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DNA damage response pathway and the apoptosis pathway were activated in LEMD2 cardiac-specific knockout mouse hearts. DNA damage was confirmed by immunofluorescence staining on heart sections and isolated cardiomyocytes, which showed upregulation of γ-H2AX [45]. In 2023, Chen et al. demonstrated that in LEMD2-mutated mouse cardiomyocytes or Hela-cells, sustained nuclear envelope rupture led to the leakage of DNA repair factors into the cytoplasm, triggering cell cycle arrest. Nuclear envelop rupture also exposed genomic DNA to the cytosol, activating the cGAS/STING/IFN pathway. As a consequence, the activation of cGAS/STING/IFN signaling drove the production of senescence-associated secretory phenotype factors, leading to cellular senescence [47].

3.1.3. Diabetic Cardiomyopathy

Diabetic cardiomyopathy is a distinct heart condition that arises from diabetes-induced changes in heart structure and function, independent of other cardiovascular risk factors like hypertension or coronary artery disease. It is marked by myocardial hypertrophy, inflammation, fibrosis, and cellular death [48,49]. Patients with diabetic cardiomyopathy will eventually develop heart failure if left untreated [50]. Unlike other forms of cardiomyopathy, diabetic cardiomyopathy is uniquely tied to metabolic disturbances, including enhanced fatty acid utilization and increased oxidative stress, making it a challenging condition to treat and manage [48,51,52].

In 2022, Ma et al. first reported increased mtDNA in the cytosol and activation of the cGAS/STING pathway in an obesity-related DCM model [53]. Transmission electron microscopy revealed significant alterations in mitochondrial structure, and an increased amount of free cytosolic mtDNA was detected by both co-immunolabeling and qRT-PCR. Meanwhile, cGAS and STING, as well as their downstream targets, NF-κB, IRF3, and IL-1β, were activated in the hearts of diabetic mice at both mRNA and protein levels detected by both co-immunolabeling and qRT-PCR. To demonstrate that mtDNA alone can activate cGAS, they transfected purified mtDNA into H9C2 cells and performed western blot and qRT-PCR analyses on those cells. Several components, such as cGAS, STING, IL-1β and IL-18, were upregulated upon mtDNA stimulation. In addition, they were able to show increased STING aggregation to the Golgi apparatus, indicating STING was functionally activated by the mtDNA treatment. Both genetic and pharmacological inhibition of STING rescued cardiac dysfunction, improved myocardial hypertrophy and fibrosis, and reduced inflammation in this mouse model of diabetic cardiomyopathy [53]. Almost at the same time, another research group pointed out that in a mouse model of diabetic DCM, oxidative damage to the mitochondria from lipid toxicity led to the release of mtDNA into the cytosol, subsequently activating the cGAS/STING pathway. In addition, they showed NLRP3 inflammasome-dependent pyroptosis and pro-inflammatory response were also activated as downstream pathways, which eventually caused myocardial hypertrophy in diabetic DCM [54]. Based on these findings, researchers began to find therapies for diabetic DCM. In 2022, Lu et al. found that cardiomyocyte-specific overexpression of Meteorin-like hormone (Metrnl) ameliorated the phenotypes of diabetic cardiomyopathy via activation of the autophagy pathway and inhibition of the cGAS/STING pathway. Mechanistically, Metrnl-induced ULK1 phosphorylation promoted the dephosphorylation and mitochondrial translocation of STING, where it formed a complex with tumor necrosis factor receptor-associated factor 2 (TRAF2). This interaction accelerated the ubiquitination and degradation of STING, ultimately making cardiomyocytes more susceptible to autophagy activation [55]. In 2023, another research group reported that irisin, by activating mitochondrial ubiquitin ligase (MITOL/MARCH5) and suppressing NLRP3 inflammasome through cGAS/STING pathway, rescued the cardiac dysfunction in diabetic cardiomyopathy [56]. In 2024, Chen et al. found that deficiency of Brahma-related gene 1, also known as SMARCA4, resulted in the accumulation of cytoplasmic dsDNA and triggered cGAS/STING activation, exacerbating cardiomyocyte inflammation and apoptosis induced by hyperglycemia and hyperlipidemia in diabetic cardiomyopathy [57]. At the same time, Huang et al. showed that both recombinant IL-37 administration and inducing IL-37 expression could alleviate cardiac dysfunction and myocardial fibrosis in diabetic DCM mice, providing a novel therapeutic

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target for the disease. Interestingly, they proposed that during the pathogenesis of diabetic DCM, hyperglycemia aggravated mitochondrial damage through SIRT1/AMPK/PGC1α signaling, leading to cell death and the release of extracellular vesicles which contains mtDNA. Fibroblasts then engulf these mtDNA-enriched vesicles, activating TLR9 signaling and the cGAS/STING pathway to initiate pro-fibrotic process and cardiac remodeling. IL-37 exerted its therapeutic effects by inhibiting these events [58].

3.2. Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM), also known as arrhythmogenic right ventricular cardiomyopathy/dysplasia, comprises a broad category of primary myocardial disorders that manifest as ventricular arrhythmias, heart failure, and sudden cardiac death [59]. The majority of ACM is caused by genetic mutations affecting desmosomal proteins, such as Desmoplakin (DSP), Plakophilin-2 (PKP2), Desmocollin-2 (DSC2), Desmoglein-2 (DSG2), Junction Plakoglobin (JUP), etc. Other genetic factors include mutations in non-desmosomal proteins, such as Phospholamban (PLN), Transmembrane Protein 43 (TMEM43), and Cadherin-2 (CDH2) [60–63].

Transmembrane protein 43 is a highly conserved membrane protein localizing to the inner membrane of the nucleus and may have an important role in maintaining nuclear envelope structure [64,65]. In 2021, Rouhi et al. found that TMEM43 haploinsufficiency is linked to the activation of the DNA damage response and the TP53 pathway, leading to increased expression of the senescence-associated secretory phenotype and pro-fibrotic factors in cardiomyopathy. cGAS and STING1, part of the DNA damage response pathway, were only activated at a later stage of the disease, which is consistent with the observed late onset of cardiac phenotypes [66].

3.3. Doxorubicin-Induced Cardiomyopathy

Doxorubicin, an anthracycline antibiotic, is commonly used to treat breast cancer, lymphomas, and leukemias [67]. Doxorubicin works by DNA intercalation, generating reactive oxygen species (ROS) and inducing apoptosis in cancer cells [68]. However, a major concern regarding the clinical use of doxorubicin and other anthracyclines is their cardiotoxicity [69–71]. Doxorubicin-induced cardiomyopathy (DIC) exhibits morphological and functional characteristics similar to those of dilated cardiomyopathy. Current hypotheses for the pathogenesis of DIC include oxidative stress, mitochondrial dysfunction, DNA damage, calcium overload, and inflammation [72]. Dexrazoxane, which chelates iron and reduces ROS formation, is the only approved medication for DIC [73–75]. Recent evidence suggests cGAS/STING-mediated inflammation might be involved in the pathogenesis of DIC [21,22,76].

DIC exists in two forms: acute and chronic. Acute DIC occurs within hours to weeks after administration, while chronic DIC develops months to years later. The pathophysiology of acute DIC mainly involves direct myocardial toxicity, oxidative stress, and inflammatory responses [77]. Chronic DIC, on the other hand, is characterized by chronic oxidative stress, mitochondrial dysfunction, persistent DNA damage, and fibrosis [69]. In 2023, Xiao et al. demonstrated a significantly increased protein level of cGAS/STING in an acute DIC mouse model and showed that STING knockdown prolonged survival and improved cardiac function. Morphological examinations of the heart revealed a reduction in the vacuolation of the myofibrils and the number of myofibrils in mice with STING knockdown. In addition, STING inhibition reduced apoptosis and inflammation in cardiomyocytes. Specifically, a reduced ratio of C-Caspase3 to T-Caspase3, a lower ratio of BAX to BCL2, fewer TUNEL-positive cells, and lower levels of pro-inflammatory cytokines, were seen in STING knockdown mice [76]. In a chronic DIC mouse model, Luo et al. first showed the activation of the cGAS/STING pathway in the heart, and global cGAS or STING knockout prevented DIC. More importantly, they noted that the activation of cGAS/STING was seen in cardiac endothelial cells and macrophages instead of cardiomyocytes and fibroblasts. Endothelial cell-specific STING knockdown rescued DIC and endothelial cell dysfunction. Specifically, cGAS/STING triggered endothelial cell inflammation and regulated mitochondrial dysfunction via CD38-induced nicotinamide adenine

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dinucleotide depletion in endothelial cells. In addition, the cGAS/STING pathway of cardiac endothelial cells also regulated cellular injury and cardiomyocyte mitochondrial bioenergetics via CD38 ecto-NADase-mediated cardiomyocyte NAD decline [21].

3.4 Sepsis-Induced Cardiomyopathy

Sepsis is a life-threatening syndrome characterized by a systemic inflammatory response to infection [78,79]. The inflammatory response may cause multiple organ dysfunctions if not controlled properly80. Sepsis-induced cardiomyopathy (SIC) develops when cardiac function is impaired during sepsis. Unlike many other types of cardiomyopathies, SIC is usually reversible with the resolution of sepsis and appropriate treatment [81,82].

In 2019, Li et al. first disclosed that STING-IRF3 could trigger lipopolysaccharide (LPS)-induced cardiac dysfunction, inflammation, apoptosis, and pyroptosis by activating NOD-like receptor protein 3 in SIC. STING deficiency could ameliorate these pathological events and improve cardiac function and overall survival. Mechanistically, LPS injection did not alter the expression level of the STING protein but promoted its perinuclear translocation and the nuclear translocation of IRF3. Knockdown of STING inhibited phosphorylation and nuclear translocation of IRF3, thus alleviating the pathological events triggered by IRF3 [83]. In contrast to their findings, Kong et al. showed that the protein expression of STING was indeed increased after LPS injection and its activation was also facilitated. They identified a novel role for Islet cell autoantigen 69 (ICA69) as a positive regulator of STING in the pathogenesis of septic cardiac injury. They discovered significant colocalization of ICA69 and STING in both cardiac tissue and macrophages and found that Ica69 knockdown can mitigate LPS-induced cardiac damage by inhibiting STING-mediated inflammation and ferroptosis [84]. In 2023, Liu et al. observed upregulation of cGAS and STING in the cardiac tissue of LPS-treated mice [85]. In addition, they found that in normal H9C2 cells, silencing of cGAS did not affect the expression levels of cGAS downstream targets, including STING, IRF3, and TBK1. However, in LPS-stimulated H9C2 cells, the expression levels of these proteins were significantly reduced when cGAS was blocked. Furthermore, following cGAS knockdown, inflammation, apoptosis, and excessive ROS production induced by LPS were also alleviated. In summary, the cGAS/STING pathway also plays a significant role in the development and maintenance of cardiomyopathy in SIC [85].

3.5. Other Cardiomyopathies

Carnitine acetyltransferase (CRAT) is a mitochondrial enzyme that catalyzes the conversion of acetyl-CoA to acetylcarnitine, which is then transferred out of the mitochondria [86]. CRAT is important in regulating cellular energy metabolism, and its deficiency leads to mitochondrial dysfunction [87,88]. In a fibroblast-specific CRAT silencing model, mitochondrial DNA was found to be released into the cytosol and activated downstream cGAS/STING/NF-κB signaling [89]. In 2023, Mao et al. generated a cardiomyocyte-specific Crat-deficient mouse model and observed the phenotypes of dilated cardiomyopathy. They also showed that depletion of Crat promoted the release of mitochondrial DNA into the cytoplasm via the mitochondrial permeability transition pore (mPTP) and triggered the cell-intrinsic type I interferon response in myocytes. Multiple cytosolic RNA and DNA sensors, including cGAS, Ddx58, Ifih1, and Aim2, were activated. Knockdown of cGAS reduced interferon-stimulated genes (ISGs) expression, inhibited AIM2 inflammasome activation, and improved cardiac contractile function in CRAT-deficient DCM [90].

Chagas cardiomyopathy is a form of cardiomyopathy resulting from Trypanosoma cruzi infection. The pathological features include myocardial inflammation, fibrosis, and severe arrhythmias [91–93]. In Chagas cardiomyopathy, Choudhuri et al. showed that extracellular vesicles from Trypanosoma cruzi-infected cells lead to increased levels of IL-1β, IL-6, and TNF-α in macrophages. In addition, with the use of cGAS inhibitor PF-06928215, a significant reduction in the levels of IL-1β, IL-6c, and TNF-α were detected [94].

Stress cardiomyopathy, also known as Takotsubo cardiomyopathy or broken heart syndrome, occurs when a person experiences acute emotional or physical stress that leads to a sudden reversible weakening of the myocardium. A massive surge of catecholamines, such as adrenaline and

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norepinephrine, has been suggested as a major mechanism for this disease. Cardiac inflammation, as a consequence of catecholamine surge, has been documented to exacerbate myocardial injury and contribute to disease progression [95–98]. In 2024, Wang et al. showed in a stress cardiomyopathy mouse model, following acute catecholamine surge, necrotic death was triggered in cardiomyocytes, which then released self-DNA and other damage-associated molecular patterns (DAMPs) [99]. These molecules were recognized by macrophages and activated cytosolic DNA-sensing pathways inside macrophages. STING, as a key component of the DNA-sensing pathway, subsequently triggered inflammatory responses in these macrophages, promoting the release of pro-inflammatory factors, such as TNF, IL-6, and CCL2, eventually leading to myocardial inflammation and injury. They believed self-DNA served as a bridge between myocyte necrosis and macrophage activation. Interestingly, the DNA sensors involved in the process were not limited to cGAS. RNA sequencing revealed several other DNA sensors, including Ddx41, Ddx58, and Zbp1, were also upregulated at the transcriptional level [99].

4. Molecular Intervention and Potential Targets on cGAS/STING Pathway in Cardiomyopathy

4.1. Molecular Intervention on cGAS/STING Pathway in Cardiomyopathy

During the last decades, different animal models have been developed to investigate the pathomechanisms involved in cardiomyopathy, which has contributed substantially to our understanding of the function of the cGAS/STING pathway in cardiomyopathy pathology. Through a literature review of experiments investigating cardiomyopathy, we found a significant activation of the cGAS/STING pathway in the cardiomyopathy group (DCM and HCM) compared to the control group (non-failing hearts, NF). Moreover, inhibition of the cGAS/STING pathway can significantly slow down disease progression. In particular, cGAS and STING inhibitors show therapeutic benefits in various cardiomyopathies. A detailed list of these compounds and their mechanisms of action are chronologically summarized in ***Table 2***.

Table 2. Molecular intervention of cGAS/STING pathway in cardiomyopathy.

Target	Compound / Drug	Mode of action	Effects on signalling cascades and in animal models	Testing systems	Disease to be investigated in the animal model:	Ref
cGAS	RU-compounds (RU.365, RU.521)	catalytic site inhibitor	reduced expression levels of *Ifnb1* mRNA in *Trex* knockout mice (which constitutively activate cGAS) · ↓ IL-1β, ↓ cleaved caspase-3 · ↓ apoptosis	*In vivo*: Trex1$^{-/-}$ mice *In vitro*: Neonatal rat cardiomyocytes (NRCMs)	multi-organ inflammation Diabetic cardiomyopathy	[20]
	Antimalarial drugs (*i.e.* Hydroxychloroquine, Quinacrine)	disrupting dsDNA binding	Hydroxychloroquine and Quinacrine inhibit dsDNA binding to cGAS *in vitro:* ↓ IFN-β expression *In vivo:* ↓ early IFN-1 response in Hydroxycloroquine-treated mice	*In vitro*: THP1-Dual cells *In vivo:* *C57BL/6 mice UVB inflammation model*		[21]

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	Suramin	disrupting dsDNA binding	suramin inhibits dsDNA binding to cGAS *in vitro* THP1-Dual cells: ↓ IFN-β expression (mRNA and protein)	*In vitro*: THP1-Dual cells		[22]
	Acetylsalicylic acid	cGAS acetylation and inhibition	↓ IFN-production in vitro (THP-1 cells) and ↓ expression of interferon-stimulated genes (ISG) Trex1$^{-/-}$ bone marrow cells; ↓ ISG expression in the hearts of Trex1$^{-/-}$ mice	*In vitro:* - THP-1 cells - Trex1$^{-/-}$ bone marrow *In vivo:* Trex1$^{-/-}$ mice	multi-organ inflammation	[23]
STING and TBK1	Astin C	STING inhibition-targeting the cyclic dinucleotide binding site	↓ expression of Ifnb, Cxcl10, Isg15, Isg56 and Tnf mRNA in the heart of Trex1$^{-/-}$ mice (in vivo); ↓ expression of type 1 interferone in Trex1$^{-/-}$ bone marrow cells (in vitro)	*In vivo*: Trex1$^{-/-}$ mice *In vitro*: Trex1$^{-/-}$ bone marrow cells	multi-organ inflammation	[24]
	Nitrofuran derivatives - C176 and C178	STING inhibition – Covalent binding to cysteine residue 91, inhibiting palmitoylation and activation of STING	↓ serum levels of type I interferons and IL-6 in Trex1$^{-/-}$ mice	*In vivo*: Trex1$^{-/-}$ mice	multi-organ inflammation	[25]
			↓ phosphorylation of p65 ↑ improve diastolic cardiac function ↑ Partially improve myocardial hypertrophy	*In vivo*: db/db mice *In vitro:* H9C2 rat cardiomyocytes	Diabetic cardiomyopathy	[26]
			↓ cardiac IRF3 phosphorylation, IRF3 nuclear translocation and CD38 expression. ↑ cardiomyocyte NAD levels, mitochondrial function and ↑ left ventricular systolic function. ↓ cardiomyocyte apoptosis. ↓ antitumor effects of doxorubicin	*In vivo*: Tumor free doxorubicin treated mice	Doxorubicin-induced cardiomyopathy (DIC)	[27]
			· ↓ IL-1β, cleaved caspase-3; · no effect on γ-H2AX; · ↓ apoptosis	· In vitro: Neonatal rat cardiomyocytes (NRCMs)	Diabetic cardiomyopathy	[28]
	Amlexanox	TBK1 inhibitor	Same effect as C176	*In vivo*: Tumor free doxorubicin treated mice	Doxorubicin-induced cardiomyopathy (DIC)	[29]

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3-acylaminoindole derivative - H-151	STING inhibition – blocking the activation-induced palmitoylation and clustering of STING	↓ calf thymus DNA-induced production of TNF in a dose-dependent manner	*In vitro:* calf thymus DNA-stimulated RAW264.7 cells (DMXAA stimulated – STING activator)	Stress cardiomyopathy (SCM)	[30]
		↓ reduced IFN-β levels in a dose-dependent manner	*In vitro:* RAW264.7 cells stimulated with recombinant murine (rm) CIRP		[31]
Ginsenoside Rb1	major chemical constituent of ginseng; suppressing the activation of STING	↓ STING-mediated proinflammatory activation of macrophages. ↓ myocardial fibrosis and inflammatory responses in the heart. ↓ DNA-triggered proinflammatory activation of macrophages. ↓ DNA-triggered whole-genome gene expression alterations in macrophages;	*In vivo:* OVX-ISO mice; *In vitro:* calf thymus DNA-stimulated RAW264.7 cells (DMXAA stimulated – STING activator)	Stress cardiomyopathy (SCM)	[32]
DMXAA	STING agonist	↑STING phosphorylation. ↑TNF, IL6, CCL2, IFN-β;	· In vitro: RAW264.7 cells	Stress cardiomyopathy (SCM)	[33]

4.2. Mitochondrial Alteration as a Hotspot for cGAS/STING Pathway Activation

As demonstrated in ***Figure 1***, damaged mitochondria can release endogenous DNA and lead to subsequent activation of the cGAS/STING pathway. By performing bioinformatic analyses using publicly available human single-cell RNA-seq data by Chaffin et al. [100], we found that mitochondrial DNA is significantly reduced in the cardiac muscle cell in the cardiomyopathy group (DCM and HCM) when compared to the control group (non-failing hearts, NF) (see ***Figure 2***). Similarly, a most recent study by Wang et al. showed that mitochondrial function-related pathways (e.g., mitochondrial matrix, mitochondrial inner membrane, mitochondrial respiratory chain complex I, oxidative phosphorylation, and electron transport chain) were found to be significantly downregulated in a stress cardiomyopathy mouse model [99]. These pilot studies shed light on the importance of mitochondrial balance in the pathogenesis of cardiomyopathies. The specific receptors responsible for recognizing mitochondrial DNA in the activation of the cGAS/STING signaling pathway in cardiomyopathy pathology have yet to be identified. Targeting mitochondrial dysfunction presents a promising therapeutic target to preserve mitochondrial balance, prevent excessive cGAS-STING activation, and ultimately avert a severe type I interferon immune response.

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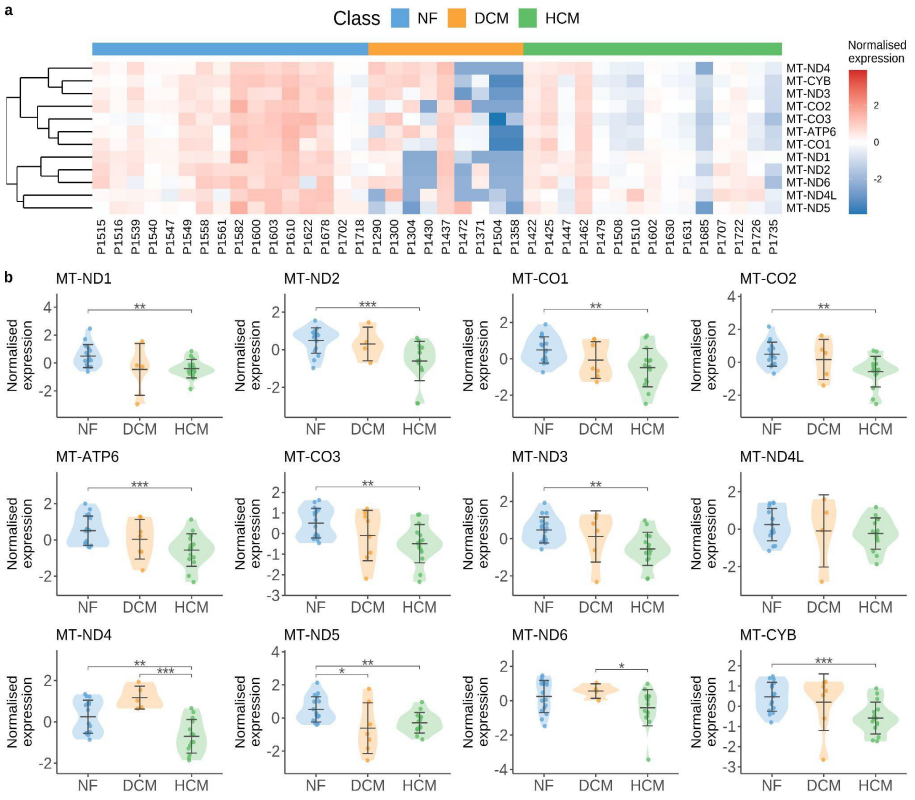

Figure 2. Mitochondrial alterations in human cardiomyopathy. (a) Heatmap displays the normalized expression of mitochondrial genes in cardiac muscle cells, which are averaged across individuals. (b) Violin plots of mitochondrial genes across different disease groups showing normalized expression value. Violin plots are centered around the mean value with standard deviation, and the shape represents sample distribution. P values are determined by Mann–Whitney U test (only significant P values are shown, *P < 0.05, **P < 0.01, ***P < 0.001). NF, non-failing hearts; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.

4.3. Future Perspectives in Understanding the cGAS/STING Pathway in Cardiomyopathy

Since Chen's group at the University of Texas Southwestern Medical Center discovered the cGAS/STING pathway, cGAS has been identified as a cytosolic DNA sensor that triggers interferon production [9,10]. However, the exact role of the cGAS/STING pathway in cardiomyopathy remains unclear. To better understand this, the following questions need to be answered. (i) Does DNA damage directly promote disease progression or is it just a reflection of late-stage damage to cardiomyocytes and progressive cardiomyocytes loss? (ii) How is the cGAS/STING pathway activated and regulated in myocytes compared to other cell types during cardiomyopathy (e.g., macrophages, fibroblasts, endothelial cells)? what is the specific downstream targets of cGAS during the cytodegeneration of cardiac muscle cells (iii) Considering mtDNA is capable of triggering cGAS/STING pathway during cardiomyopathy [101], it would be intriguing to understand how the mtDNA is released into the cytosol and whether this released mtDNA in the cyotosol could be targeted as a therapeutic approach during cardiac failure?

Last but not least, we deem it mandatory to point out that it is of particular interest to consider the cGAS/STING pathway under the context of aging and senescence during disease progression. The aging and elderly population is particularly susceptible to cardiovascular diseases. Age is an independent risk factor for cardiomyopathy [102]. Elderly patients usually suffer from both neurodegenerative and cardiovascular diseases, and the comorbidity worsens clinically relevant outcomes, including the severity of disability at diagnosis and rate of disability worsening after diagnosis103. Further investigation is warranted to determine if the cGAS/STING pathway serves as the cornerstone in regulating chronic cardiomyopathy.

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Abbreviations

The following abbreviations are used in this manuscript:

DCM	Dilated cardiomyopathy
HCM	Hypertrophic cardiomyopathy
cGAS	cyclic GMP-AMP synthase
STING	Stimulator of interferon genes
TBK1	TANK-binding Kinase 1
IRF3	interferon regulatory factor 3
dsDNA	double-stranded DNA

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