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Review

The cGAS-STING Pathway: A New Therapeutic Target for Ischemia–Reperfusion Injury in Acute Myocardial Infarction?

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Abstract: The innate immune system is the body's natural defense system, which recognizes a wide range of microbial molecules (such as bacterial DNA and RNA) and abnormal molecules within cells (such as misplaced DNA, self-antigens) to play its role. DNA released into the cytoplasm activates the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) signaling pathway to initiate an immune response. Ischemia–reperfusion injury (IRI) after acute myocardial infarction refers to the phenomenon where myocardial tissue suffers further damage upon the restoration of blood flow. This issue is a significant clinical problem in the treatment of myocardial infarction, as it can diminish the effectiveness of reperfusion therapy and lead to further deterioration of cardiac function. Studies have found that the cGAS-STING signaling pathway is closely related to this phenomenon. Therefore, this review aims to describe the role of the cGAS-STING signaling pathway in ischemia–reperfusion injury after myocardial infarction and summarize the current development status of cGAS-STING pathway inhibitors and the application of nanomaterials to further elucidate the potential of this pathway as a therapeutic target.

Keywords: cGAS-STING; acute myocardial infarction; ischemia–reperfusion injury; inhibitors of cGAS-STING; nanomaterial technology

Citation: Tian, M.; Li, F.; Pei, H. The cGAS-STING Pathway: A New Therapeutic Target for Ischemia–Reperfusion Injury in Acute Myocardial Infarction? *Biomedicines* **2024**, *12*, 1728. https://doi.org/10.3390/biomedicines12081728

Academic Editors: Jun Lu, Enrico Gugliandolo, Rosanna Di Paola and Roberta Fusco

Received: 4 July 2024
Revised: 18 July 2024
Accepted: 31 July 2024
Published: 2 August 2024

1. Backgrounds

Cytosolic nucleic acid sensors, as pattern recognition receptors (PRRs), play a crucial role in initiating innate immune responses against pathogens. These sensors activate the immune response by recognizing abnormal cytosolic nucleic acids, such as viral or bacterial DNA and RNA [1,2]. The cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway, as a key mechanism for sensing cytosolic DNA, activates and induces immune responses by recognizing nucleic acids that are absent or abnormally present in host cells. This pathway plays a significant role in anti-infective defense, autoimmune and inflammatory diseases, and cancer immunotherapy [3]. The cGAS-STING signaling pathway is an important component of the innate immune host defense system, particularly in detecting intracellular DNA and inducing type I interferon responses [4]. However, its role in inflammatory diseases is complex; it can provide protection by activating the innate immune system, but excessive or abnormal activation may lead to pathological inflammatory responses [5,6].

Cardiovascular diseases are one of the leading causes of death worldwide, with acute myocardial infarction (AMI) being a significant component. Its high incidence and mortality rates impose a heavy burden on healthcare systems. Myocardial infarction typically requires urgent vascular reperfusion and drug therapy to restore myocardial blood supply promptly [7,8]. However, post-reperfusion, there is often a phenomenon of further myocardial damage, which is a significant factor contributing to patient mortality and

increasing the risk of heart failure [8]. After a period of ischemia, the myocardium often experiences subsequent damage upon the re-establishment of blood flow, known as ischemia–reperfusion injury [9,10]. This refers to the damage caused to tissues or organs when blood supply is restored (reperfusion) after a period of interruption (ischemia). This process is commonly observed in clinical scenarios like myocardial infarction and stroke, and the injury can result from various mechanisms such as oxidative stress, inflammatory responses, and cell apoptosis [11].

Research has shown that when tissues experience ischemia, leading to ischemic injury, the subsequent reperfusion process may trigger the activation of the cGAS-STING pathway. This activation could enhance inflammatory responses, induce cell apoptosis, and promote damage propagation, thereby exacerbating tissue injury [12–14]. Due to the significant role of the cGAS-STING pathway in ischemia–reperfusion (IR) injury, researchers have begun to explore therapeutic strategies targeting this pathway. This article summarizes the mechanistic role of cGAS-STING in acute myocardial infarction and subsequent IR injury, while also describing the current status of therapeutic approaches targeting the STING pathway in IR injury using inhibitors and nanomaterials targeting cGAS or STING, aiming to evaluate the potential of the cGAS-STING signaling pathway in myocardial infarction treatment.

2. The Activation of the cGAS-STING Signaling Pathway

The activation process of the cGAS-STING pathway is a complex and precise signaling cascade, primarily involving the interaction and activation of two key proteins, cGAS (cyclic GMP-AMP synthase) and STING (stimulator of interferon genes).

cGAS is a cytoplasmic DNA sensor that plays a crucial role in immune regulation by recognizing and binding to foreign DNA, such as viral DNA or DNA released from cell damage, inside and outside the cell. When cells are infected by viruses, experience cellular damage, or encounter DNA release from other sources, cGAS can identify and bind to these foreign DNA molecules [15]. Upon binding to foreign DNA, cGAS undergoes conformational changes and activation, leading to the activation of its nucleotidyltransferase activity. Activated cGAS then synthesizes cyclic GMP-AMP (cGAMP) from GTP and ATP in the cytoplasm, which serves as a secondary signaling molecule. cGAMP is an important signaling molecule that acts as a second messenger to further activate the STING signaling pathway [16–18].

The STING protein is a critical immune signaling molecule located on the endoplasmic reticulum (ER) membrane. Its N-terminus features four transmembrane domains that anchor STING to the ER membrane [19]. Following the transmembrane region is a long cytoplasmic domain containing the cGAMP binding domain and the signaling domain, which can specifically bind to cGAMP molecules. When cGAMP binds to STING, it promotes the oligomerization of STING, causing multiple STING molecules to aggregate into oligomers. This leads to the transport of STING from the endoplasmic reticulum to the Golgi apparatus, followed by its phosphorylation by tank-binding kinase 1 (TBK1) [20,21]. Phosphorylated TBK1 can recruit and activate interferon regulatory factor 3 (IRF3), which then translocates into the nucleus to induce the expression of interferon and inflammatory genes [22,23].

Activated STING not only activates IRF3 but also can activate IκB kinase (IKK). The activated IKK complex phosphorylates IκBα (the NF-κB inhibitory protein), and the phosphorylated IκBα is subsequently ubiquitinated and degraded. This degradation releases NF-κB (such as the p65/RelA and p50 subunits) from IκBα. The released NF-κB then translocates to the nucleus, where it binds to specific DNA sequences and initiates the transcription of inflammatory genes [24–26].

Upon activation, the cGAS-STING pathway enhances the host cell's antiviral state by releasing type I interferons and activating NF-κB. This response collectively boosts the cell's ability to combat infections, while also recruiting and activating immune cells to

eliminate the infection. This pathway effectively regulates the immune response, defends against infections, and maintains intracellular homeostasis [18,27] (Figure 1).

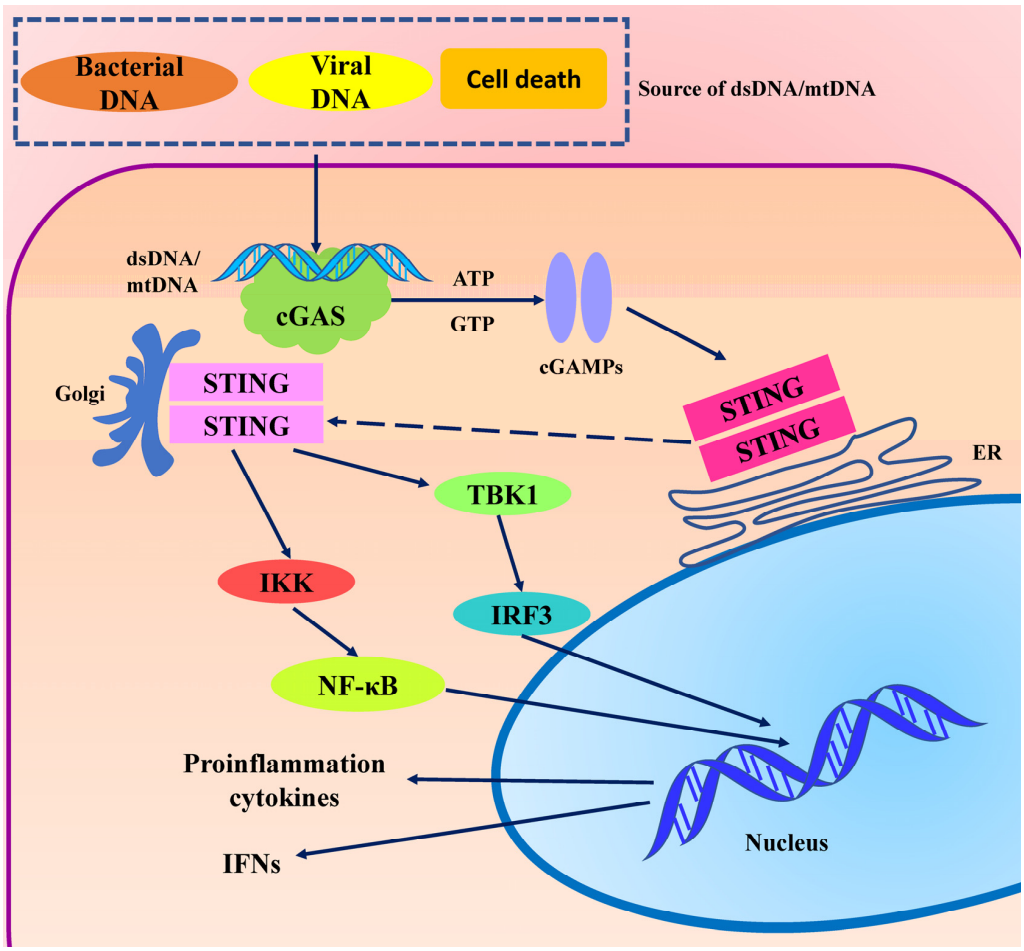

Figure 1. Activation mechanism of the cGAS-STING signaling pathway. When DNA damage occurs within cells (such as through viral infection, DNA destruction, or leakage of nuclear DNA), it results in a cellular environment rich in dsDNA fragments. These DNA fragments are detected by intracellular cGAS. Once cGAS detects DNA, it undergoes a conformational change, forming an active conformation. This active conformation allows for the binding of two ATP molecules and one GTP molecule to form cGAMP. The synthesized cGAMP is released by cGAS into the cytoplasm, where it binds to STING. Subsequently, STING also undergoes a conformational change, enabling it to bind to TBK1. The binding of TBK1 to STING activates TBK1, leading to the phosphorylation and activation of IRF3. Activated IRF3 translocates into the nucleus and cooperates with other transcription factors to promote the transcription and expression of type I interferon (IFN-I) genes. The activation of STING also triggers the activation of the NF-κB pathway. This activation may occur through a series of molecular events, such as the activation of IKK (IκB kinase), leading to the degradation of IκB (inhibitor of NF-κB protein), thereby releasing NF-κB and promoting its translocation into the nucleus, ultimately activating the transcription of NF-κB-responsive genes.

3. The Role of cGAS-STING in Myocardial Infarction Injury

Reperfusion therapies such as percutaneous coronary intervention (PCI) and thrombolytic therapy are crucial measures to reduce mortality in patients with AMI [28]. Timely reperfusion can decrease the area of myocardial cell necrosis, lower the acute phase mortality of AMI, and restore myocardial function in the damaged area [29]. After a myocardial infarction, the acute inflammatory response aims to clear necrotic cells and tissue debris, which is the first step in myocardial repair. An appropriate inflammatory response helps initiate the repair process and promotes healing. However, excessive or prolonged in-

flammation can lead to secondary damage, compromising healthy myocardial tissue and resulting in cardiac dysfunction and heart failure [30]. To mitigate ischemia–reperfusion injury following myocardial infarction, scientists and clinicians are exploring various interventions. Nevertheless, ischemia–reperfusion injury after myocardial infarction remains a significant clinical challenge.

The inflammatory response after AMI is an important but complex process for restoring cardiac function, involving various cellular and molecular mechanisms. The cGAS-STING pathway plays a critical role in this process by regulating immune and inflammatory responses. Myocardial infarction leads to the ischemic necrosis of myocardial cells, resulting in cell membrane rupture and the release of intracellular DNA and mitochondrial DNA into the cytoplasm [31]. This cytoplasmic DNA is recognized by intracellular cGAS, which activates STING. The activated STING promotes the expression of type I interferons (such as IFN-β) and pro-inflammatory cytokines (such as TNF-α, IL-6, and IL-1β), further activating local and systemic immune responses [32]. The activated cGAS-STING pathway not only recruits inflammatory cells (such as neutrophils, macrophages, and monocytes) to the infarcted area, releasing more inflammatory mediators and exacerbating myocardial injury, but also induces myocardial fibrosis through a prolonged inflammatory response [33]. This fibrosis leads to scar tissue formation, reducing myocardial elasticity and contractile function and increasing the risk of heart failure.

AMI leads to the necrosis of myocardial cells and the release of cytoplasmic DNA, which is recognized by cGAS in the cytoplasm [34]. Studies have reported an increase in the STING protein in the infarcted heart tissue of animal models of AMI, highlighting its involvement in the post-MI inflammatory response. Hypoxia-induced cardiomyocyte and fibroblast death contributes to the upregulation of STING in macrophages, establishing the role of STING in intercellular signaling during myocardial infarction [35]. The absence of Large Tumor Suppressor 2 (Lats2) protein can inhibit mitochondrial fission and inactivate the STING/p65 signaling pathway by preventing hypoxia-induced mitochondrial DNA (mtDNA) release into the cytosol [36].

Single-cell sequencing results from samples of infarcted and non-infarcted mouse hearts indicate that during the inflammatory response triggered by MI, a specific group of interferon-inducing cells (IFNICs) within cardiac macrophages produce large amounts of type I interferons and interferon-stimulated genes (ISGs) via the cGAS-STING-IRF3 axis, initiating and maintaining a strong inflammatory response [37]. The study also found that mice lacking cGAS, STING, IRF3, or the type I interferon receptor IFNAR showed impaired ISG expression. In these genetically deficient mice, the expression of inflammatory cytokines and chemokines was reduced, cardiac inflammatory cell infiltration was decreased, ventricular dilation was lessened, cardiac function was significantly improved, and survival rates were notably higher after MI. Treatment of MI mouse models with IFNAR-neutralizing antibodies similarly inhibited the interferon response, improved left ventricular dysfunction, and increased survival rates. This indicates the critical role of the cGAS-STING-IRF3 axis in the inflammatory response and cardiac function following MI [38–40]. Meanwhile, other studies have found that in a mouse model of myocardial infarction, the STING inhibitor H-151 shows significant effects in restoring myocardial function and reducing cardiac fibrosis [41]. Additionally, in vitro cell experiments have demonstrated that H-151 can alleviate the type I interferon response induced by cardiac dsDNA in bone marrow-derived macrophages (BMDMs). Consequently, H-151 can reduce apoptosis in adult cardiomyocytes and fibrosis in cardiac fibroblasts [42].

In summary, the role of cGAS in reperfusion injury following myocardial infarction primarily involves sensing released cytosolic DNA and activating the cGAS-STING pathway, which leads to inflammatory responses and immune cell involvement, ultimately exacerbating myocardial injury. Therefore, targeting the cGAS-STING pathway could offer new strategies for treating reperfusion injury (Figure 2).

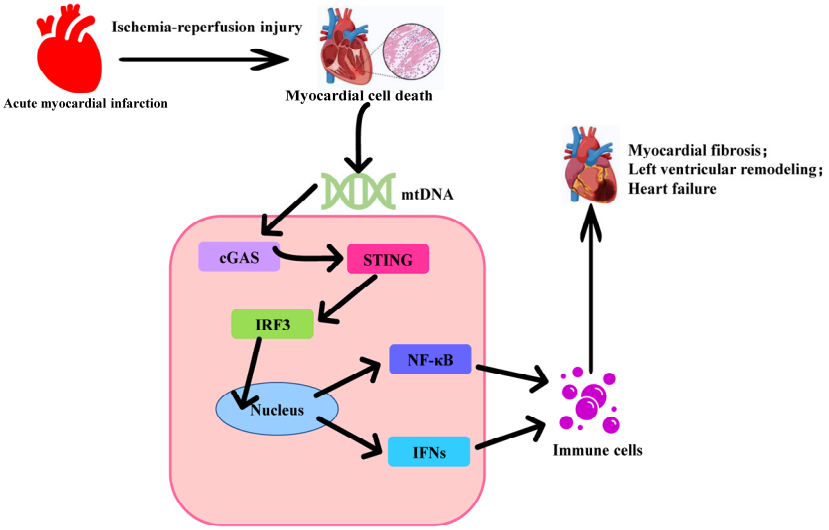

Figure 2. Mechanism of cGAS-STING activation in acute myocardial infarction reperfusion injury. During acute myocardial infarction and reperfusion, myocardial cells undergo necrosis or apoptosis due to ischemia and oxidative stress, leading to the release of mitochondrial and nuclear DNA into the cytosol. This cytosolic DNA is recognized and bound by cGAS, which activates the cGAS-STING signaling pathway, triggering a series of downstream signaling events, including the phosphorylation and nuclear translocation of interferon regulatory factor 3 (IRF3) and nuclear factor κB (NF-κB). These inflammatory factors induce a robust inflammatory response through autocrine or paracrine pathways, further activating and recruiting immune cells such as neutrophils, macrophages, and T cells to the damaged area. This persistent inflammation and microcirculatory dysfunction ultimately lead to cardiac dysfunction, manifested by myocardial fibrosis, left ventricular remodeling, and an increased risk of heart failure.

4. Inhibitors of the cGAS-STING Signaling Pathway

The critical roles of the cGAS and STING pathways in innate immunity and inflammatory responses make them a focal point of pharmacological research, particularly in the development of small-molecule inhibitors [23,43]. These compounds aim to antagonize cGAS and STING to control unnecessary inflammation and acute tissue damage caused by their chronic activation. This review seeks to find a balance to maximize the protective effects of these pathways while minimizing their potential harmful impacts.

cGAS inhibitors work by interfering with the cGAS activity, preventing it from producing cGAMP, thereby inhibiting the downstream STING pathway and reducing the production of interferons and pro-inflammatory cytokines. cGAS inhibitors are mainly classified into three types: direct inhibitors, competitive inhibitors, and antisense oligonucleotides [44–46]. Direct inhibitors bind to cGAS, blocking its enzymatic activity. These inhibitors include RU.521 and G150. RU.521 is a selective cGAS inhibitor that directly binds to cGAS, inhibiting its catalytic activity and showing significant inhibitory effects in vitro by reducing DNA-induced interferon production. G150 is a novel small-molecule inhibitor that binds to cGAS and inhibits its activity. It has demonstrated effective cGAS inhibition in both in vitro and in vivo experiments, reducing the levels of inflammatory factors [47]. Competitive inhibitors inhibit cGAS activity by competing with its substrate for binding. These inhibitors include drugs such as PF-06928215. PF-06928215, developed by Pfizer, is a competitive cGAS inhibitor currently in preclinical studies [48–51]. Research shows that this inhibitor effectively suppresses cGAS activity in animal models, alleviating symptoms of various inflammatory diseases. Antisense oligonucleotides work by binding to mRNA, inhibiting cGAS expression. This class of inhibitors includes IONIS-cGAS. IONIS-cGAS is an antisense oligonucleotide targeting cGAS mRNA, reducing cGAS production by inhibiting its expression [52–54]. This drug has shown significant anti-inflammatory effects in animal models and is currently in preclinical studies. In summary, although multiple cGAS

inhibitors have demonstrated promising results in preclinical studies, no cGAS inhibitor has yet entered large-scale clinical trials (Table 1).

Table 1. Classification and characteristics of cGAS inhibitors.

Classification	Name	Features	Limitations
Direct inhibitors	RU.521	Highly selective, capable of effectively inhibiting cGAS activity and reducing DNA-induced interferon production.	Clinical application data are limited, and there may be issues with specificity and pharmacokinetics.
	G150	A novel small molecule that directly binds to cGAS and inhibits its activity. It has shown good efficacy both in vitro and in vivo.	It is in the preclinical stage and requires further research to confirm its long-term safety and efficacy.
Competitive inhibitors	PF-06928215	Shows potential for various autoimmune and inflammatory diseases.	It is in the preclinical research stage and has not yet entered clinical trials.
Antisense oligonucleotides	IONIS-cGAS	Targets cGAS mRNA, reduces cGAS protein levels, and has shown significant anti-inflammatory effects in animal models.	Delivery and stability of antisense oligonucleotides are challenging, requiring solutions for cellular uptake and degradation issues.

STING inhibitors also have significant potential in treating autoimmune and inflammatory diseases. These inhibitors can block STING activation or interfere with its interaction with downstream effector molecules. Based on their chemical structure, STING inhibitors are mainly classified into small-molecule STING inhibitors and natural-product STING inhibitors [55]. Small-molecule inhibitors are chemically synthesized compounds that inhibit STING activation by directly binding to STING or interfering with its key functional regions. The developed small-molecule inhibitors include H-151, C-176, C-178, SN-011, and GSK3745417. H-151 is a compound that directly binds and inhibits STING by interfering with its dimerization and downstream signaling. Studies have shown that H-151 can effectively reduce STING-mediated inflammatory responses and has demonstrated good therapeutic effects in various disease models [56,57]. C-176 and C-178 are covalent inhibitors of STING, forming covalent bonds with specific sites on STING to inhibit its activity; both have shown effective anti-inflammatory effects in vitro and in vivo [58]. SN-011 is a small-molecule inhibitor that binds to STING's active site, preventing its interaction with cGAMP and thereby inhibiting STING activation [59]. Research indicates that SN-011 effectively suppresses inflammatory responses in mouse models. GSK3745417 is a STING inhibitor developed by GSK. It is an orally available small molecule that binds to the STING protein and inhibits its activity, thereby blocking normal STING signal transduction [60]. This modulates the production of interferons and related immune cytokines, regulating immune responses. Natural-product STING inhibitors are compounds with STING-inhibitory activity extracted from nature. These compounds typically have complex chemical structures and are derived from plants, microorganisms, or other organisms, showing potential for modulating immune responses. Common natural-product STING inhibitors include Astin C and flavonoids. Astin C is a polysaccharide natural product extracted from seaweed (red algae) with anti-inflammatory and immunomodulatory activity [61]. Flavonoids are a class of natural products found in many plants, such as citrus fruits, tea leaves, and grapes. Certain flavonoids have been discovered to possess STING-inhibitory activity, such as reducing STING-mediated interferon production [62,63]. These natural products can inhibit the STING signaling pathway, reducing interferon production and immune responses. In conclusion, research on STING inhibitors is still ongoing, and further clinical and laboratory validation is needed to assess their potential and safety in treatment (Table 2).

Table 2. Classification and characteristics of STING inhibitors.

Classification	Name	Features	Limitations
Small-molecule STING inhibitors	H-151	High specificity, good drug tunability, and easy manufacturing and modification.	Potential off-target effects, poor metabolic stability, and high clinical trial risks.
	C-176		
	C-178		
	SN-011		
	GSK3745417		
Natural-product STING inhibitors	Astin C	Multifunctionality, lower toxicity, and good biocompatibility.	Difficulty in large-scale production through synthetic means; lower stability and bioavailability.
	Flavonoids		

5. The Application of Nanomaterial Technology

The application of nanomaterial technology in cGAS-STING inhibition is an emerging and promising research field. Nanomaterials possess unique physicochemical properties and biocompatibility, allowing them to be designed and prepared as carriers or delivery systems with specific functions for delivering cGAS or STING inhibitors to regulate the cGAS-STING signaling pathway [64,65]. Nanomaterial technology also holds potential for applications in treating myocardial infarction (MI), especially by modulating immune responses to alleviate myocardial damage and promote repair [66–69].

Zheng et al.'s research developed a multifunctional crosslinked hydrogel system, significantly enhancing myocardial wall thickness in a rat MI model by inhibiting macrophage STING signaling pathway activation, improving cardiac function, and myocardial regeneration [70]. The study suggests that nanomaterial technology has tremendous potential in treating MI and offers certain clinical translational benefits. It is important to note that while nanomaterial technology holds vast prospects in treating cardiovascular diseases and immune regulation, it still faces many challenges in applications such as the biocompatibility of nanomaterials, targeting, drug release control, and so on [71]. Therefore, combining nanomaterial technology with cGAS-STING pathway inhibitors for treating myocardial infarction requires further research and clinical validation.

6. Conclusions

Cytosolic nucleic acid sensors are a class of receptor molecules capable of recognizing and responding to intracellular nucleic acids, playing a crucial role in innate immunity. cGAS is an important cytosolic DNA sensor that plays a crucial role in the innate immune response. When it detects exogenous DNA in the cytosol, it generates cyclic GMP-AMP (cGAMP) to activate the STING pathway, which in turn induces the production of type I interferons and other inflammatory factors.

Acute myocardial infarction (AMI) is an acute cardiac condition for which reperfusion therapy is a key treatment. However, reperfusion itself can cause additional tissue damage, known as reperfusion injury. This injury can lead to myocardial cell death, inflammatory responses, and impaired cardiac function. Ischemia–reperfusion injury following myocardial infarction can activate the cGAS-STING pathway, resulting in the release of interferons and inflammatory factors, which trigger the infiltration and activation of inflammatory cells, affecting cardiac function and patient prognosis.

Studies have shown that inhibiting cGAS or STING activity in animal models reduces the severity of ischemia–reperfusion injury following myocardial infarction. Currently, the development of cGAS-STING inhibitors is an active area of research. Advances in nanomaterial technology can further address the shortcomings of cGAS-STING inhibitors, enhancing their clinical application prospects. Additionally, therapeutic strategies targeting the cGAS-STING pathway can be combined with other treatments, such as anti-inflammatory and antioxidant therapies, to form a comprehensive multi-target treatment strategy.

Overall, with a deeper understanding of the mechanism of action of the cGAS-STING pathway, inhibiting the activity of cGAS or STING is a promising research direction. It can provide new strategies and methods for treating myocardial infarction, and with further research and clinical validation of cGAS-STING inhibitors, they have the potential to become a new option for the treatment of ischemia–reperfusion injury following myocardial infarction, improving patient prognosis and quality of life. In the future, personalized treatment plans can be implemented based on individual patient conditions and immune characteristics for precise treatment. However, further research and clinical trials are still needed to verify their safety and efficacy for widespread clinical use.

Author Contributions: M.T., H.P. and F.L. offered the main direction and significant guidance of this manuscript. M.T. drafted the manuscript and illustrated the figures and tables for the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare that they have no competing interests.

Abbreviations

PRRs	pattern recognition receptors
cGAS	cyclic GMP–AMP synthase
STING	stimulator of interferon genes
AMI	acute myocardial infarction
IR	ischemia–reperfusion
dsDNA	double-stranded DNA
cGAMP	cyclic GMP-AMP
ER	endoplasmic reticulum
TBK1	tank-binding kinase 1
IKK	inhibitor of kappa B kinase
IRF3	interferon regulatory factor 3
IFN	interferon
NF-kB	nuclear factor kappa B
TAK1	TGF-beta-activated kinase 1

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