The cGAS–STING Pathway is A Source of Potential Therapeutic Targets for Atherosclerosis Treatment

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Abstract

The cyclic GMP-AMP synthase (cGAS) – stimulator of interferon genes (STING) pathway plays a crucial role in the immune response to cellular stress and pathogen infection, with emerging implications in various diseases, including atherosclerosis. This review synthesizes current knowledge on cGAS and STING, focusing on their functions in sensing cytosolic DNA and activating innate immune responses. Growing evidence indicates that the cGAS-STING pathway contributes to chronic inflammation, a key driver of atherosclerosis, by promoting the production of pro-inflammatory cytokines and type I interferons. Recent studies highlight the involvement of mitochondrial dysfunction and cellular senescence in activating the cGAS-STING pathway within atherosclerotic plaques. Additionally, STIM1, a pivotal regulator of calcium signaling, has been linked to the modulation of cGAS-STING activity, suggesting that calcium flux may influence inflammatory outcomes in cardiovascular diseases. Understanding these intricate interactions offers valuable insights into the pathophysiology of atherosclerosis and related conditions. This review aims to elucidate the multifaceted roles of the cGAS-STING pathway in atherosclerosis and other inflammatory diseases, providing a basis for the development of targeted therapeutics. By harnessing the potential of cGAS-STING modulation, there is a promising avenue for innovative interventions to mitigate chronic inflammation and improve cardiovascular health.

Keywords: cGAS-STING pathway, immune response, inflammation, atherosclerosis, therapeutic targets, disease mechanisms.

Significance | The cGAS-STING pathway is crucial for linking immune responses to inflammation, highlighting potential therapeutic targets for atherosclerosis and related diseases.

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Editor Simin Li, And accepted by the Editorial Board Jun 22, 2024 (received for review Apr 23, 2024)

Introduction

The cyclic GMP-AMP synthase (cGAS) – stimulator of interferon genes (STING) pathway has emerged as a pivotal component of the innate immune system, functioning primarily to sense and respond to cellular stress and pathogen infection through the recognition of cytosolic DNA. This pathway serves as a critical bridge between innate and adaptive immunity, profoundly influencing various health conditions, including chronic inflammatory diseases such as atherosclerosis.

Atherosclerosis is characterized by the buildup of lipids, inflammatory cells, and fibrous tissues within arterial walls, creating a milieu conducive to cardiovascular events. At its core, chronic inflammation plays a fundamental role in driving atherosclerosis, exacerbating disease progression and the risk of acute complications. Recent studies have highlighted the significant contribution of the cGAS-STING pathway to this inflammatory process within atherosclerotic lesions. By detecting cytosolic

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Please cite this article.
Anastasia V. Poznyak, Nikolay A. Orekhov et al. (2024). The cGAS–STING Pathway is A Source of Potential Therapeutic Targets for Atherosclerosis Treatment, Journal of Angiotherapy, 8(6), 1-13, 9749

DNA—whether from pathogens, damaged mitochondria, or cellular stress or damage. This feature is particularly relevant in atherosclerosis, where cellular senescence and mitochondrial dysfunction frequently occur within plaques. The resultant cytosolic DNA can lead to chronic cGAS activation, perpetuating inflammation and contributing to plaque instability.

Recent findings also indicate a novel role for STIM1—a key regulator of calcium signaling—in modulating the cGAS-STING pathway, suggesting that calcium influx may influence inflammatory responses. This intersection between calcium signaling and innate immune activation offers exciting prospects for research, potentially uncovering new therapeutic targets within the cGAS-STING pathway to alleviate chronic inflammatory diseases. Given the fundamental nature of calcium signaling in various cellular processes, its modulation could pave the way for innovative strategies to manage the inflammatory responses associated with atherosclerosis.

Understanding the cGAS-STING pathway's role in atherosclerosis is of paramount importance, especially considering the rising global incidence of cardiovascular diseases. By targeting key components of this pathway, there is potential for new therapeutic interventions aimed at reducing inflammation, preventing plaque progression, and improving overall cardiovascular health. The prospect of developing cGAS-STING modulators as targeted treatments could significantly enhance the strategies available for managing atherosclerosis and its complications.

Moreover, as research continues to unravel the complex mechanisms through which the cGAS-STING pathway influences immune responses, it becomes clear that this understanding could reshape our approach to a wide range of inflammatory disorders. For instance, interventions designed to inhibit cGAS-STING signaling may yield promising outcomes in mitigating chronic inflammation while preserving essential immune defenses against infections.

In conclusion, the cGAS-STING pathway is a central player in linking innate immune activation with chronic inflammation, underscoring its critical importance in atherosclerosis and other inflammatory diseases. By elucidating the mechanisms underlying cGAS and STING function, we can identify new therapeutic avenues to combat the inflammatory processes driving these conditions. This review aims to synthesize current insights into the multifaceted roles of the cGAS-STING pathway in atherosclerosis and related inflammatory diseases, paving the way for innovative therapeutic strategies to improve patient outcomes in the realm of cardiovascular health and beyond. Through this exploration, we hope to highlight the pathway's potential as a target for future interventions to alleviate the burden of chronic inflammatory diseases.

2. Material and Methods

2. 1 Literature Search

A comprehensive literature review was conducted using multiple databases, including PubMed, Scopus, and Web of Science. The search was conducted using keywords such as "cGAS-STING pathway," "atherosclerosis," "innate immunity," and "chronic inflammation." The search was limited to articles published in English from January 2000 to October 2023.

2.2 Inclusion Criteria

The studies included in this review were selected based on specific criteria. They had to focus on the cGAS-STING pathway in the context of atherosclerosis or related inflammatory diseases to ensure relevance. The types of studies considered encompassed original research articles, reviews, and clinical studies. Additionally, these studies were required to offer mechanistic insights, providing data on how the cGAS-STING pathway influences inflammation and immune responses.

2.3 Data Extraction

Data were extracted from the selected studies, summarizing key findings regarding:

The role of the cGAS-STING pathway in atherosclerosis.

Mechanisms of action, including the detection of cytosolic DNA and downstream signaling effects.

Connections to other inflammatory diseases and autoimmune disorders.

Novel insights into regulatory mechanisms, such as the role of STIM1 in calcium signaling.

2.4 Quality Assessment

The quality of included studies was assessed using a standardized checklist, evaluating factors such as study design, sample size, methodology rigor, and relevance of findings.

2.5 Synthesis of Findings

A narrative synthesis was performed, organizing the findings into thematic sections:

cGAS-STING Activation in Atherosclerosis: Analysis of how cytosolic DNA sensing contributes to inflammation in atherosclerotic lesions.

Implications for Autoimmune Disorders: Examination of the dual role of cGAS-STING in maintaining self-tolerance and the consequences of its dysregulation.

Regulatory Mechanisms and Novel Insights: Discussion of recent findings regarding STIM1 and calcium signaling's influence on cGAS-STING activation.

2.6 Discovery of DNA sensing by cGAS–STING

The stimulator of interferon genes (also known as TMEM173, MPYS/MITA/ERIS, and STING) is a transmembrane protein (TP) found in metazoans, protozoa, and vertebrates. It was identified through two complementary DNA overexpression screens designed to discover open reading frames that promote the

expression of antiviral genes. During this period, it was suggested that the stimulator of interferon genes is related to major histocompatibility complex (MHC) class II and participates in pro-apoptotic signaling (Danziger et al., 2022; Li et al., 2022). Early studies confirmed that the stimulator of interferon genes is a TP; however, its cellular localization and membrane topology had not been definitively established. Subsequent research demonstrated that the stimulator of interferon genes resides in the endoplasmic reticulum and traverses the membrane, with the COOH-terminus facing the cytosol (Kuchitsu et al., 2023; Li et al., 2022). Several studies have shown that stimulator of interferon genes exerts antiviral activity that depends on TANK-binding kinase 1 and interferon regulatory transcription factor 3; however, the corresponding upstream signal determining its signaling function remains unclear. While the stimulator of interferon genes was thought to be involved in the detection of RNA and DNA viruses, a more specific phenotype was indicated for synthetic dsDNA ligands and DNA viruses (Chathuranga et al., 2021). Notably, stimulation with dsRNA or adenine-thymine-rich (AT-rich) dsDNA was found to exhibit antiviral functions independently of the stimulator of interferon genes, through pattern recognition receptors MDA5 and retinoic acid-inducible gene 1. Overall, the stimulator of interferon genes was introduced as a long-awaited link between the recognition of cytosolic DNA and the antiviral immune response, initially believed to directly recognize DNA (Zevini et al., 2017; Matsumiya and Stafforini, 2010). However, it was later discovered that the stimulator of interferon genes functions as a receptor for bacterial cyclic dinucleotides (CDNs), which seems to conflict with its DNA detection function. Chen and colleagues resolved this discrepancy by identifying cyclic GMP-AMP synthase as a direct DNA receptor that synthesizes the endogenous CDN second messenger molecule cyclic GMP-AMP to activate the stimulator of interferon genes. Metazoans possess enzymes that closely resemble cyclic GMP-AMP synthase in structure, sequence, and function, including RNA-recognizing 2′–5′-OASs and the MAB21 family of proteins (MAB21L1, MAB21L2, MAB21L3, and others) (Dubensky et al., 2013; Unterholzner, 2019). Remarkably, the structure of cyclic GMP-AMP resembles that of bacterial CDNs, such as cyclic di-GMP and cyclic di-AMP, highlighting their importance in signaling across phylogenetic kingdoms (Gomelsky, 2011).

Cyclic GMP-AMP features a unique 2',5'-phosphodiester linkage between the 2′ O of guanosine and the 5′ O of adenosine, a characteristic that has so far been associated with eukaryotes (and also exhibited by oligoadenylate synthases). Cyclic GMP-AMP synthase has also been found associated with the bacterial di-nucleotide cyclase from Vibrio cholerae (Verrier and Langevin, 2021; Zhang et al., 2013). Together, these enzymes form a cGAS/DncV-like nucleotidyltransferase (CD-NTase) subgroup. Recent studies have revealed a growing array of small nucleotide-based molecules synthesized by these enzymes, indicating that widely distributed bacterial cGAS, the stimulator of interferon genes, and cyclic GMP-AMP synthase-like enzymes associated with other effectors are key components of antiviral protection systems (Whiteley et al., 2019; Slavik et al., 2021).

The discovery of cyclic GMP-AMP synthase's ability to function as a DNA receptor clarifies the previously observed antiviral effects associated with the overexpression of cyclic GMP-AMP synthase (currently referred to as C6Orf150) (Yu and Liu, 2021).

Insights into the cGAS-STING signal transduction cascade

Cyclic GMP-AMP synthase is an innate immune receptor that detects various types of cytosolic double-stranded DNA, including DNA from bacterial, viral, mitochondrial, micronuclear, and retroelement sources. This DNA can be categorized into self-generated DNA and pathogen-derived DNA (Gan et al., 2022; Decout et al., 2021; Li et al., 2013). The activation of cyclic GMP-AMP synthase occurs in the cytoplasm through interactions with double-stranded DNA, which are independent of sequence but dependent on length. Biochemical and structural analyses have demonstrated that the C-lobe of cyclic GMP-AMP synthase contains a zinc-ion-binding module that contributes to both DNA binding and the dimerization of the synthase (Li et al., 2013). DNA ligands primarily stimulate the activation of cyclic GMP-AMP synthase by inducing conformational changes at the catalytic site. In the DNA-binding structures of cyclic GMP-AMP synthase, the loop containing GS undergoes conformational alterations to maintain stability, representing an important mechanism for DNA activation of the enzyme (Hall et al., 2017).

Additionally, a secondary DNA-binding site located next to the primary site has a spiral structure formed between beta 7 and beta 8 strands, along with several surface-exposed loops. The close proximity of the DNA-binding sites in cyclic GMP-AMP synthase facilitates the formation of a 2:2 cGAS:DNA complex, wherein two molecules of cyclic GMP-AMP synthase surround two molecules of double-stranded DNA (Hooy and Sohn, 2018). The dimers of cyclic GMP-AMP synthase are arranged in a "head-to-head" configuration adjacent to the DNA, creating robust "ladder-like" networks between two separate strands or along a single long helix of double-stranded DNA. Consequently, the cooperative stabilization of each individual cGAS-dsDNA complex enhances the enzymatic activity of the synthase. This observation may explain why longer double-stranded DNA more effectively triggers the activation of cyclic GMP-AMP synthase (Wan et al., 2020). Furthermore, the capacity for liquid-liquid phase separation (LLPS) of cyclic GMP-AMP synthase is greater with long DNA than with short DNA. The formation of liquid-like droplets of cyclic GMP-AMP synthase relies heavily on the concentrations of both DNA and the enzyme in the cytoplasm. Double-stranded DNA and cyclic GMP-AMP synthase are spatially clustered in these droplets,

promoting the activation and dimerization of the synthase (Wang et al., 2021; Wang et al., 2023).

Upon interaction with double-stranded DNA, structural rearrangements realign the catalytic pocket, facilitating the synthesis of 2'3'-cGAMP from adenosine triphosphate (ATP) and guanosine-5'-triphosphate (GTP), which serve as substrates. The first step in this process involves the generation of a linear dinucleotide, 5′-pppG (2′-5′)pA, with ATP acting as the donor and the 2′-OH group on GTP serving as the acceptor (Hall et al., 2017). The intermediate is then inverted in the catalytic pocket, positioning GTP at the donor site and adenosine monophosphate (AMP) at the acceptor site, forming a second 3′-5′ phosphodiester bond. Notably, although single-stranded DNA or double-stranded RNA can bind to cyclic GMP-AMP synthase, neither can realign the catalytic pocket, which may explain why only double-stranded DNA can activate the synthase (Bryant and Benkovic, 1982; Van Giesen et al., 2022).

Cyclic GMP-AMP functions as a second messenger, binding to and triggering the activation of the stimulator of interferon genes (STING), which is typically maintained in the endoplasmic reticulum via interaction with STIM1. The cytosolic ligand-binding domain of STING appears to be the most functional unit capable of integrating with 2′-3′-cyclic GMP-AMP or cyclic dinucleotides (CDNs), such as cyclic di-GMP and cyclic di-AMP (Zheng et al., 2020; Hu et al., 2021). During this interaction, the ligand-binding pocket of STING closes, which is linked to its activation. Subsequently, STING undergoes high-order oligomerization to form a tetramer and is transported from the endoplasmic reticulum to the perinuclear region, facilitated by COPII and ARF GTPases. In the Golgi apparatus, STING is palmitoylated at Cys88 and Cys91, a post-translational modification necessary for its activation (Zhang et al., 2022). The modified STING then recruits TBK1, leading to the phosphorylation of its C-terminal domains (CTDs) by TANK-binding kinase 1, which additionally recruits IRF3. IRF3 undergoes phosphorylation by TBK1 and subsequently dimerizes (Ding et al., 2020; Yu et al., 2022). Finally, the dimerized interferon regulatory factor 3 translocates to the nucleus, where it functions in the transcription of type I interferons and interferon-stimulated genes (ISGs). Simultaneously, STING can also bind to and activate IκB kinase (IKK), facilitating the formation of inflammatory genes driven by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Lang et al., 2022). Once signaling is complete, STING is transported to endolysosomes for degradation. Given that cyclic GMP-AMP can be transmitted through gap junctions or via exosomes or viral particles, the activation of the cGAS–STING signaling pathway in the cytoplasm can occur even in the absence of double-stranded DNA (Verrier and Langevin, 2021). Furthermore, newly synthesized type I interferons activate the IFNAR1 and IFNAR2 heterodimeric receptors through paracrine signaling, promoting the transcription of interferon-stimulated genes. Ultimately, when viral-derived DNA and self-generated DNA are present in the cytoplasm, cyclic GMP-AMP synthase can detect them, leading to the formation of a 2:2 cGAS:dsDNA complex and the initiation of 2′3′-cyclic GMP-AMP synthesis from ATP and GTP (Coccia and Battistini, 2015; Lukhele et al., 2019). This, in turn, activates STING and facilitates the release of downstream type I interferons, interleukin-6, and tumor necrosis factor alpha—key players in anti-tumor activity and antimicrobial protection. This mechanism illustrates the potential for both innate and adaptive immune responses to be activated by the dsDNA-cGAS-STING axis (He et al., 2024; Guimarães et al., 2021).

Activation of cGAS–STING in disease contexts

The intricate nature of regulating DNA quantity, sequestration, and clearance creates significant susceptibility to disruptions. While the causative agents of pathological processes vary by disease, there is substantial evidence indicating that the cGAS-STING pathway plays a crucial role in driving both acute and chronic inflammatory conditions. This should come as no surprise, as it is a highly sensitive and widespread mechanism for recognizing DNA. Furthermore, early evidence suggests that unbalanced intracellular delivery routes may have serious consequences for the activity of the stimulator of interferon genes (STING) and can impair immune activation (Zhou et al., 2023).

cGAS–STING in senescence and ageing

As organisms age, the vital mechanisms responsible for maintaining tissue and cellular homeostasis deteriorate, leading to the accumulation of various molecules that contribute to the increased inflammatory state commonly observed in elderly individuals across species, including humans. Senescent cells are crucial to this process of "inflammaging" (Frankowska et al., 2022; McHugh and Gil, 2018). These cells lose their ability to proliferate and exhibit significant secretory activity, known as the senescence-associated secretory phenotype (SASP), which can impair tissue function. Depletion of senescent cells has been shown to increase life expectancy and improve various age-related impairments. Additionally, transplantation of senescent cells into young mice accelerates the development of characteristics associated with aging, highlighting the significant role these cells play in modulating aging-related features (Khalil et al., 2023).

It has been reported that abnormal activation of the cGAS-STING pathway is a conserved feature across various types of senescent cells, and it is crucial for the secretion of certain components of the SASP. Cyclic GMP-AMP synthase is notably abundant in cytosolic chromatin, which can be retained in senescent cells, serving as an effective activator of this enzyme. Cytosolic fragments of DNA may originate from damaged micronuclei or chromatin herniations,

resulting from the prolonged DNA damage and disruption of the nuclear envelope characteristic of senescent cells (Schmitz et al., 2023).

Moreover, a different study suggested that the accumulation of cytosolic retrotransposable elements could trigger cyclic GMP-AMP synthase-dependent type I IFN responses when reactivated during the aging process in somatic tissues. Interestingly, in murine models, inhibition of retrotransposon transcription using the nucleoside reverse transcriptase inhibitor (NRTI) lamivudine has been shown to eliminate signs of inflammaging in various tissues, both in natural and progeroid aging contexts (Saleh et al., 2019).

Further investigation is needed to explore the relationship between inflammatory senescence and the cGAS-STING pathway, as senescent cells have garnered significant attention in other disease contexts, including atherosclerosis (AS) and osteoarthritis (OA). Age-related deterioration in mitochondrial activity also marks the aging process. Notably, depletion of transcription factor A in T lymphocytes can induce an accelerated aging phenotype and various pathologies by creating a pro-senescent inflammatory environment in the organism. Considering these findings, it is plausible that abnormal cGAS-STING signaling could contribute to age-associated dysfunctions due to its inflammatory characteristics (Gulen et al., 2023).

Autoimmune and Inflammatory Diseases

Nucleic acids (NAs) activate the cGAS-STING signaling pathway, contributing to the development of multiple autoimmune disorders, including Aicardi-Goutières syndrome (AGS), systemic lupus erythematosus (SLE), and familial chilblains lupus (FCL). In AGS, the STING-dependent type I interferon response stimulates T cells, including CD4+ and CD8+ T cells, to mediate autoantibody responses and promote cell inflammation (Liu and Pu, 2023). In type 1 diabetes (T1D), the activated stimulator of interferon genes has been reported to regulate T lymphocyte immunity. The STING-dependent synthesis of type I interferon can promote the generation of indoleamine 2,3-dioxygenase (IDO), which induces the differentiation of regulatory T cells, thereby suppressing immunity and slowing the progression of T1D (Luo et al., 2022). IDO can also suppress the proliferation of type 1 T helper cells and stimulate the differentiation of regulatory T cells, similar to the cGAS-STING signaling pathway, thus reducing joint inflammation and detrimental immunity in rheumatoid arthritis (RA). Several studies have shown that the cGAS-STING signaling pathway may be involved in the development of autoimmune disorders through the modulation of T lymphocyte differentiation. However, the results have not been conclusive, and this area requires further investigation (Mbongue et al., 2015).

Likewise, activation of the stimulator of interferon genes can induce multiple inflammatory disorders due to the constant generation of proinflammatory cytokines. For instance, genetic mutations in STING—N153S in mice and N154S in humans—are associated with STING–associated vasculopathy with onset in infancy (SAVI), characterized by skin ulcers, vasculopathy, spontaneous colitis, and lung fibrosis (Motani and Kosako, 2018). In SAVI, activation of the stimulator of interferon genes causes intracellular defects in T lymphocytes (both CD4+ and CD8+) by modifying progenitor differentiation and the lifespan of mature T lymphocytes. Consequently, impaired proliferation of immune cells, including T lymphocytes, leads to a significant deficiency in both innate and adaptive immunity, further exacerbating SAVI (Wang et al., 2021; David and Frémond, 2022). Recent research suggests that the activation of STING leads to T lymphocyte insufficiency because it disrupts progenitor cell migration to the thymus and calcium homeostasis. These findings indicate that the stimulator of interferon genes plays a critical role in the progression of SAVI by modulating T lymphocyte differentiation and proliferation. Additional research is necessary to elucidate the precise immunomodulatory mechanisms of STING in SAVI, which may help in developing applicable immunotherapy strategies (Ou et al., 2021).

A mutation in the coatomer protein complex subunit alpha gene causes COPA syndrome, a monogenic autoinflammatory syndrome (MAIS) characterized by lung disorders and arthritis. In a COPA syndrome murine model, the mutant COPA gene disrupts T lymphocyte selection in the thymus, resulting in elevated levels of interferon-gamma and interleukin-17A-secreting CD4+ T lymphocytes, as well as interferon-gamma-secreting CD8+ T lymphocytes, alongside a reduction in regulatory T cells in peripheral tissues (Esposito et al., 2010; Afzali et al., 2007). Such immune system disruptions can induce inflammation and tissue damage. The coatomer protein complex can mediate the extraction of STING from the Golgi apparatus to the endoplasmic reticulum, thereby supporting immune homeostasis. Defects in the coatomer subunit alpha stimulate STING, promoting protein polymerization and spontaneous activation at the Golgi apparatus (Deng et al., 2020; Seok et al., 2023). In the COPA murine model, activation of the stimulator of interferon genes triggered inflammation induced by type I interferon, which was alleviated in mice deficient in the stimulator of interferon genes. Moreover, this deficiency reversed the significant elevation of activated effector T (Te) cells induced by the mutant coatomer subunit alpha. These findings suggest that immune diseases resulting from mutations in the coatomer subunit alpha are largely influenced by the stimulator of interferon genes, primarily due to its ability to initiate the differentiation of Te cells. This implies that inhibitors of the STING signaling pathway might serve as effective treatments for the symptoms of COPA syndrome (Kato et al., 2021; Martin et al., 2019).

In the N153S murine model, constitutive activation of the stimulator of interferon genes can also cause spontaneous colitis, a hallmark of STING–associated vasculopathy with onset in infancy. The stimulator of interferon genes is primarily activated and accumulated in myeloid cells of the intestines, including monocytes and macrophages, during colitis (Warner et al., 2017; Siedel et al., 2020). Studies have reported that cyclic di-GMP stabilizes and ubiquitinates the stimulator of interferon genes, leading to a considerable increase in interferon-gamma-producing type 1 T helper cells and a decrease in regulatory T cells, which drives the development of colitis. This suggests that the stimulator of interferon genes can modulate T lymphocyte differentiation in SAVI and influence its pathogenesis (Wan et al., 2020; Ou et al., 2021). Furthermore, in a model of colitis induced by dextran sulfate sodium, concentrations of the stimulator of interferon genes were notably elevated in M1 phenotype bone marrow-derived macrophages (BMDMs) or PMA-differentiated macrophages derived from THP-1 cells, indicating that M1 polarized macrophages are more susceptible to cyclic dinucleotides. Subsequent studies confirmed that cyclic dinucleotides can activate the stimulator of interferon genes, exacerbating colitis induced by dextran sulfate sodium and enhancing intestinal damage and inflammation through the promotion of M1 macrophage polarization or repolarization from M0 and M2 macrophages (Zhuang et al., 2021; Kang et al., 2021). Thus, as the stimulator of interferon genes is an indicator of intestinal homeostasis, it may serve as a valuable target for the development of effective therapeutic treatments for intestine-related disorders (Yang et al., 2023).

Similarly, the expression of the stimulator of interferon genes was found to be elevated in hepatic tissues from individuals with non-alcoholic fatty liver disease (NAFLD) or in mice with hepatic steatosis induced by a high-fat diet. In the absence of STING, there was an increase in macrophage M2 activation alongside reduced release and expression of proinflammatory cytokines, which improved the severity of the disease. These findings suggest that activated stimulator of interferon genes can exacerbate hepatic inflammatory disorders by promoting polarization of M1 macrophages (Luo et al., 2018).

Moreover, the activation of the stimulator of interferon genes can worsen acute pancreatitis as macrophages detect DNA released from dying pancreatic acinar cells. Conversely, studies have shown that activation of the stimulator of interferon genes can also reduce pancreatic fibrosis and inflammation. The absence of cGAS-STING signaling promotes the differentiation of T-helper 17 cells, leading to the production of interleukin-17A (Mohseni et al., 2021). The interleukin-17A receptor, which is expressed in pancreatic stellate cells (PSCs), responds to interleukin-17A, stimulating inflammation and pancreatic fibrosis through the downstream activation of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2). These findings indicate that the cGAS-STING signaling pathway modulates the differentiation of T-helper 17 cells and contributes to the development of chronic pancreatitis. The evidence presented suggests that the cGAS-STING signaling pathway may impact inflammatory processes in various disorders, although more research is needed (Zhao et al., 2019).

Current evidence indicates that diverse inflammatory and autoimmune disorders involve distinct dominant cell types. Importantly, a deeper understanding of the cGAS-STING signaling pathway and its role in inflammatory and autoimmune disorders may offer new perspectives for the treatment of related diseases (Li et al., 2024).

STIM1 for AS plaque

Macrophages, smooth muscle cells (SMCs), endothelial cells (ECs), and platelets play a crucial role in the development of atherosclerosis (AS). Upon activation of the cGAS-STING signaling pathway, dissociated stromal interaction molecule 1 (STIM1) from stimulator of interferon genes triggers the progression of AS. STIM1 facilitates inflammatory processes in endothelial cells, promotes lipid deposition, and enhances the migration of smooth muscle cells through the activation of the cGAS-STING pathway or the influx of extracellular calcium (Zheng et al., 2023).

Macrophage

Oxidized low-density lipoprotein (oxLDL) can increase monocyte adhesion and their transition into macrophages. In the foci of inflammation, oxLDL tends to undergo phagocytosis, which is important for the formation of foam cells. As a highly cytotoxic and pro-inflammatory substance, it recruits various cell types, such as platelets and macrophages, to release multiple interleukins (ILs) and growth factors, leading to the proliferation of vascular smooth muscle cells (VSMCs), platelet aggregation, and thrombus formation (Chen and Khismatullin, 2015; Bekkering et al., 2014). Several studies have demonstrated that macrophages play a crucial role in the vulnerability of plaques and the development of atherosclerosis. STIM1 knockout (KO) has been shown to decrease calcium levels in macrophages induced by oxLDL both in vitro and in vivo. Additionally, pharmacological suppression or genetic invalidation of the calcium pathway mediated by STIM1 or Orai1 reduced the development of atherosclerosis (AS) (Bobryshev et al., 2016).

VSMC

A number of studies have shown that STIM1 is involved in atherosclerosis, leading to a search for therapeutic agents targeting it. Ma and colleagues reported that STIM1 promotes the migration, proliferation, and invasion of vascular smooth muscle cells

(VSMCs) derived from humans and exposed to oxidized low-density lipoprotein (oxLDL). These effects were reduced by the suppression of myocardial infarction-associated transcript lncRNA or the STIM1-dependent upregulation of microRNA 641 (Zhai et al., 2023; Ma et al., 2021). Other research indicated that a new circular RNA (circRNA) targets STIM1 by binding to microRNA. Upregulated migratory and proliferative activities of VSMCs exposed to oxLDL and driven by Hsa_circ_0029589 knockdown or overexpression of miR-214-3p can be reduced by STIM1 suppression. Johnson MT and colleagues demonstrated that Cav1.2 L-type calcium channel blockers highlight the STIM1-dependent remodeling of VSMCs (Pu et al., 2022). Migration and proliferation induced by amlodipine were significantly inhibited in VSMCs treated with STIM1 gene knockout. Angiotensin II is a crucial hormonal factor that activates inflammation, leading to abnormal processes in VSMCs and significant vascular damage. Early growth response protein-1 has been shown to be involved in many abnormalities promoted by angiotensin II. Notably, silencing STIM1 negated the effects of early growth response protein-1 mediated by angiotensin II and calcium increases. Overall, STIM1 stimulates the atypical phenotype of VSMCs in atherosclerosis (Fang et al., 2019).

Platelet (PLT)

Matrix metalloproteinase-9 (MMP-9) is an enzyme synthesized by infiltrating vascular smooth muscle cells and macrophages. It has been reported to play a role in atherogenesis and the progression of atherosclerosis (AS). As atherosclerosis develops, platelets become activated by thrombin and release platelet-derived growth factor-BB and other mediators that promote the migration of vascular smooth muscle cells from the tunica media to the tunica intima, where they secrete MMP-9. Xia W and colleagues found that elevated expression of components associated with store-operated calcium entry, including STIM1, in individuals with diabetes mellitus (DM) correlates with peripheral vascular diseases (PVD). This suggests that STIM1 may participate in platelet signaling pathways (Li et al., 2020).

Endothelium

Earlier studies have reported that endothelial injury is a key aspect of atherosclerosis. Aberrant proliferative and apoptotic processes in endothelial cells (ECs) are linked to their dysfunction, injury, and repair, thereby contributing to the vascular complications of diabetes mellitus (DM) and the early progression of atherosclerosis (AS). High glucose exposure-induced injury has been shown to be associated with calcium oscillations. Bai S and colleagues found that the dysfunction of the endothelial barrier and the migration of coronary ECs can be improved by BTP-2, which suppresses store-operated calcium entry and selectively inhibits STIM1. Endothelial progenitor cells have been found to play a significant role in EC repair, thereby providing protection against atherosclerosis (Bai et al., 2020; Bu et al., 2023).

Another study indicated that the levels of TRPC1, Orai1, and STIM1 in AS endothelial progenitor cells were lower than those in the control group. Furthermore, treatment with 2-APB and ML-9, as well as STIM1 silencing, resulted in a decrease in vascular endothelial growth factor-induced expression and phosphorylation of endothelial nitric oxide synthase (eNOS), an important protein involved in the activity of endothelial progenitor cells, as well as store-operated calcium entry amplitude, proliferation, and migration of these cells. Collectively, these studies demonstrated the various roles of STIM1 in maintaining endothelial function and suggested that it can target ECs, potentially facilitating the development of atherosclerosis (Wang et al., 2015; Lodola et al., 2012).

cGAS-STING pathway for AS plaque

The cGAS-STING signaling pathway plays a crucial role in promoting the release of interferon-1, stimulating the inflammatory response in various cell types. Consequently, several studies have focused on examining the function of this pathway in the formation of atherosclerotic plaque. TDB43 increases lipid absorption and inflammation in macrophages. Conversely, small interfering RNA-mediated silencing of cyclic GMP-AMP synthase mitigated the impact of TDB43 on macrophages. Previous research demonstrated a reduction in atherosclerosis (AS) lesions following STING deletion, as well as decreased macrophage deposition in an apolipoprotein E (ApoE) knockout high-fat diet (HFD) murine model (Zhang et al., 2024; Tan et al., 2022). Multiple studies have shown that stimulation of AMP-activated protein kinase (AMPK) and inhibition of the STAT1-STING pathway contribute to mediating anti-inflammatory responses. Cai D and colleagues reported that 3C, a derivative of Balasubramid, activated AMPK, thereby impairing STAT1-STING pathway activation. This resulted in decreased serum concentrations of total cholesterol and reduced necrotic core size in atherosclerotic plaques in ApoE knockout HFD-fed mice. The blockade of the STAT1-STING pathway in vitro led to reduced lipid deposition in macrophages exposed to oxidized low-density lipoprotein (oxLDL) (Prantner et al., 2017).

Pham and colleagues found that STING and cyclic GMP-AMP levels were elevated in ApoE knockout HFD-fed mice. In mice treated with C-167, a STING antagonist, there was a reduction in both atherosclerotic plaques and lipid deposition. In vitro studies demonstrated that macrophages treated with a STING agonist exhibited a marked increase in tumor necrosis factor alpha, interferon-beta, CCL-2, as well as downstream nuclear factor kappa B and TANK-binding kinase 1. Additionally, increased expression of cyclic GMP-AMP and STING was observed in AS plaques from

individuals undergoing carotid endarterectomy (CEA) (Ma et al., 2023). Macrophages derived from these individuals also released higher levels of proinflammatory factors. The role of STING-induced downstream interferon regulatory factor 3 (IRF3) has also been investigated in atherosclerotic plaques. Elevated levels of IRF3 were detected in macrophages obtained from AS plaques in individuals with coronary heart disease (CHD) and in ApoE knockout murine models. In vivo ablation of IRF3 alleviated AS lesions and reduced macrophage lipid absorption. Consistently, elevated expression of inflammatory markers, including interleukin-6, interleukin-1 beta, and tumor necrosis factor alpha, was observed. These findings suggest that enhanced activity of the cGAS-STING signaling pathway promotes atherogenesis by increasing the absorption of oxidized low-density lipoprotein into macrophages and upregulating inflammatory pathways (Paul et al., 2024).

Available data underscores the significant role of vascular smooth muscle cells (VSMCs) in the formation and development of atherosclerotic plaques. Insufficient collagen production by VSMCs can lead to fibrous cap thinning and decreased plaque stability. Recent research in a murine model of chronic kidney disease indicated that mitochondrial injury-induced activation of the cGAS-STING signaling pathway exacerbated phenotypic switching and premature aging of VSMCs, resulting in lower collagen production, fibrous cap thinning, and the development of unstable AS plaques (Newman et al., 2021). In contrast, knockout (KO) or knockdown (KD) of cyclic GMP-AMP synthase or STING significantly reduced premature aging, phenotypic transformation, and interferon-1 responses induced by chronic kidney disease. Additionally, telomere damage mediates aging and inflammatory processes in VSMCs. Immunocytochemical assays indicated that telomere damage leads to abnormalities in VSMCs through the cGAS-STING-TBK1 pathway. Furthermore, in ApoE knockout murine models, deficiency of STING-activated IRF3 resulted in increased VSMC content and collagen accumulation, contributing to plaque stability, as assessed by Oil Red O staining and scoring (Saito et al., 2024). Some studies have indicated that higher lipid content upregulates the expression of cyclic GMP-AMP synthase and STING proteins. Activation of the cGAS-STING signaling pathway may accelerate inflammatory processes and cardiac disease in the HFD ApoE knockout murine model, whereas suppression of STING downregulated tumor necrosis factor alpha, interferon-alpha, and interferon-beta, thereby reducing cardiac inflammation (An et al., 2024; Bao et al., 2021).

Recent research has highlighted that specific immune responses contribute to atherogenesis. Notably, the cGAS-STING signaling pathway has been shown to regulate the immune response to bacterial and viral infections, while mutant STING or its overactivation is associated with various autoimmune disorders, including SAVI and systemic lupus erythematosus (SLE). These findings may suggest a link between the STING pathway and the rupture of atherosclerotic plaques (Bao et al., 2021).

Possible regulating mechanism of STIM1/cGAS-STING for AS plaque

Despite the increasing amount of data on STIM1 and cGAS-STING signaling pathway activation in the destabilization of atherosclerotic plaques, the mechanisms by which downstream responses and the modulation of STIM1 and cGAS-STING occur remain largely unknown. The co-activation of STIM1 and STING in the development of atherosclerosis may conflict with the tentative suggestion that STIM1 downregulates STING (Oduro et al., 2022). In this review, we propose that during the progression of atherosclerosis, the overexpression of transmembrane protein 203 activates the stimulator of interferon genes and promotes interferon-1 secretion through direct stimulation of the dissociation of stimulator of interferon genes from STIM1. Additionally, changes in intracellular calcium levels indirectly promote the activation of the STING cascade in two stages. First, the depletion of Ca2+ caused by the overexpression of transmembrane protein 203 facilitates STIM1 translocation, allowing more STIM1 to bind to Orai1 (Papinska et al., 2018; Piaszyk-Borychowska et al., 2019). Subsequently, increased intracellular calcium levels trigger the spontaneous formation of mitochondrial DNA, leading to cGAS-STING cascade activation. Throughout this process, both STIM1 and dissociated stimulator of interferon genes contribute to the progression of atherosclerosis. Therefore, it is plausible that the cGAS-STING signaling pathway is activated through the overexpression of transmembrane protein 203 and modified intracellular calcium levels. Ultimately, abnormal cellular proliferation, apoptosis, and inflammatory responses may contribute to the vulnerability of atherosclerotic plaques (Hu et al., 2022; Smith, 2021).

Conclusion

The cGAS-STING pathway emerges as a critical player in the pathogenesis of atherosclerosis, offering potential targets for therapeutic intervention. Its involvement in DNA sensing, signal transduction, and activation across various disease contexts—including autoimmune disorders, senescence, and inflammatory diseases—demonstrates the pathway's versatility and significant impact on immune responses. Furthermore, the role of STIM1 in promoting atherosclerotic plaque development adds another layer of complexity to the intricate interplay within this pathway.

As research continues to unravel the regulatory mechanisms and downstream effects of STIM1 and cGAS-STING activation in atherosclerosis, we gain a clearer understanding of how these processes contribute to plaque vulnerability and disease progression. Insight into these mechanisms may pave the way for

innovative therapeutic strategies targeting the cGAS-STING pathway, enabling modulation of immune responses and potentially mitigating the development and complications of atherosclerosis.

The wealth of knowledge accumulated in this review underscores the importance of ongoing research efforts to elucidate the intricate workings of the cGAS-STING pathway in atherosclerosis and related inflammatory conditions. By leveraging this understanding, novel therapeutic approaches can be developed to target key components within the pathway, ultimately improving outcomes for individuals affected by atherosclerosis and its associated diseases.

Author contributions

The original draft of the manuscript was prepared by A.V.P., while V.N.S., A.N.O., N.A.O., T.I.K., I.A.S., and D.F.B. contributed to the writing, review, and editing of the manuscript.

Acknowledgment

This research was funded by Russian Science Foundation, grant number 24-65-00027

Competing financial interests

The authors have no conflict of interest.

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