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ABOUT COVER

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REVIEW

Role of cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes pathway in diabetes and its complications

Ming-Wei Fan, Jin-Lan Tian, Tan Chen, Can Zhang, Xin-Ru Liu, Zi-Jian Zhao, Shu-Hui Zhang, Yan Chen

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Abstract

Diabetes mellitus (DM) is one of the major causes of mortality worldwide, with inflammation being an important factor in its onset and development. This review summarizes the specific mechanisms of the cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)-stimulator of interferon genes (STING) pathway in mediating inflammatory responses. Furthermore, it comprehensively presents related research progress and the subsequent involvement of this pathway in the pathogenesis of early-stage DM, diabetic gastroenteropathy, diabetic cardiomyopathy, non-alcoholic fatty liver disease, and other complications. Additionally, the role of cGAS-STING in autonomic dysfunction and intestinal dysregulation, which can lead to digestive complications, has been discussed. Altogether, this study provides a comprehensive analysis of the research advances regarding the cGAS-STING pathway-targeted therapeutic agents and the prospects for their application in the precision treatment of DM.

Key Words: Cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes; Diabetes mellitus; Inflammation; Glycolipid metabolism; Diabetes gastroenteropathy; Nonalcoholic fatty liver disease; Diabetes cardiovascular disease; Diabetes nephropathy

Core Tip: Inflammation mediated by the cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)-stimulator of interferon genes (STING) signaling pathway is closely related to the occurrence and development of diabetes and its complications. This article focuses on the specific mechanism of cGAS-STING signaling pathway in mediating inflammatory response as well as the role of cGAS-STING signaling in complications such as diabetes, diabetic gastroenteropathy, diabetic cardiomyopathy, and non-alcoholic fatty liver disease, along with the role of transmission pathways and the related research progress.

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INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycemia caused by multiple etiological factors. Long-term disorders of glucose and lipid metabolism can cause chronic progressive lesions, functional decline and failure of multiple systems, tissues and organs. The latest statistics in 2021, the number of people with diabetes worldwide is about 529 million, accounting for about 6.1% of the total population. Type 2 DM (T2DM) accounts for 96% of the cases, of which more than 50% of T2DM can be attributed to obesity, and lack of exercise. Complications such as diabetes cardiovascular disease, diabetes nephropathy (DNe), blindness, limb loss, disability, and chronic pain significantly reduce the quality of life of patients, and place a huge burden on public health[1].

Traditional hypoglycemic drugs including biguanides, sulfonylureas, thiazolidinediones, and gliclazones do not meet the clinical needs, with some of them exhibiting poor or unsustainable efficacy or adverse drug reactions such as hypoglycemia, weight gain, and gastrointestinal reactions. Some Food and Drug Administration-approved drugs, such as glucagon-like peptide-1 receptor agonists (such as selegiline and liraglutide), dipeptidyl peptidase-4 inhibitors (such as selegiline and viglitin), and sodium-dependent glucose transporter 2 inhibitors (such as dagliflozin), have already been applied in clinical settings. However, some drugs such as glucokinase activators, peroxisome proliferator-activated receptor (PPAR) agonists, free fatty acid (FFA) receptor 1 agonists, and menin inhibitors are still in clinical trials; and have in treatment of DM and delaying β-cell damage have greater potential. Siehler *et al*[2] identified the insulin inhibitory receptor Inceptor, a new potential target for treating DM, which increases the sensitivity of the insulin signaling pathway in pancreatic β cells and promotes their protection and regeneration. Teplizumab delays type 1 DM (T1DM) progression by binding to cluster of differentiation CD3 on effector T cells and inhibiting their action on pancreatic β cells[3]. Presently available therapeutic agents mainly slow down the damage to islet β cells and reduce lipid cell metabolism. The development of medicines and the understanding of disease pathogenesis are closely linked. Recent studies have shown that the cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS)-stimulator of interferon genes (STING) pathway plays an important role in the early and progressive stages of diabetes as well as in multiorgan complications. It is expected to be a new therapeutic target with great potential[4].

cGAS, a natural immune receptor, recognizes various double-stranded DNA (dsDNA) in the cytoplasm, including those from exogenous viruses, bacteria, endogenous mitochondria, nuclei, and reverse-transcribed DNA[5]. Following dsDNA binding, the cGAS enzyme is activated, which then catalyzes the synthesis of the second messenger cGAMP from adenosine triphosphate (ATP) and guanosine triphosphate (Figure 1). Next, cGAMP binds to the dimeric protein STING on the endoplasmic reticulum (ER) membrane, altering its conformation, triggering STING oligomerization, and its transfer to the Golgi apparatus. In the Golgi apparatus, the two cysteine residues of STING (namely Cys88 and Cys91) are palmitoylated. STING then recruits and interacts with TANK-binding kinase 1 (TBK1), which phosphorylates interferon (IFN) regulatory factor 3 (IRF3), triggering dimerization, nuclear translocation, and induction of IRF3-related target genes, thereby affecting IFN production. Recently, the cGAS-STING pathway has been reported to be involved in the pathogenesis of metabolic diseases, as cGAS can recognize dsDNA from endogenous mitochondria and induce metabolic inflammation[6].

Reportedly, the cGAS-STING pathway plays an important role in both early and progressive stages of DM and in associated multiorgan complications, and it has been proposed as a novel, potential therapeutic target. Hence, this study aims to discuss the role of the cGAS-STING pathway in DM and its subsequent complications. Additionally, the regulatory roles of the cGAS-STING pathway in DM, diabetic gastroenteropathy (DG), non-alcoholic fatty liver disease (NAFLD), diabetic cardiomyopathy (DCM), DNe, diabetic retinopathy (DR), and diabetic wound (DW) healing have been discussed. This review highlights the implications of the cGAS-STING pathway in distinct disease processes and may provide insights into the systemic management of DM. A summary of additional literature related to this research has been provided in Table 1.

CGAS-STING IN DM PATHOGENESIS

DM is a multiorgan metabolic disorder, mainly caused by absolute or relative insulin deficiency and characterized by impaired glucose tolerance and hyperglycemia. Reportedly, inflammatory pathways can lead to obesity, insulin resistance (IR), and subsequent DM-associated metabolic disorders and complications. T1DM is an autoimmune disease characterized by the autoimmune elimination of pancreatic islet β cells, resulting in insulin deficiency. In animal models, immune cells have been implicated in T1DM progression. T cells can induce an inflammatory infiltration around the islet β cells and DM, and macrophages mediate islet inflammation and secretion of inflammatory factors interleukin (IL)-1β and tumor necrosis factor (TNF)-α, which are associated with the synergistic effects of IFN-γ that result in apoptosis of pancreatic β cells[7]. T2DM is characterized by a relative insulin deficiency because of the development of IR in organs such as the liver, muscle, and other major organs that are not sensitive to insulin. Fat accumulation in the liver and muscle tissues is a precursor to IR, and related adipokines (such as leptin and adiponectin) mediate inflammatory responses, allowing immune cell infiltration in adipose tissues. Altogether, these factors substantially increase the inflammatory response in the body, ultimately leading to DM-associated organ damage and dysfunction[8], suggesting that regulating local inflammatory cytokine production may control the development of DM.

cGAS-STING in T1DM pathogenesis

T1DM is an autoimmune disease characterized by β cell destruction, mainly by free radical and oxidant production leading to DNA damage and activation of an apoptotic cascade triggered by polyadenosine diphosphate-ribose polymer (PARP) activation[9]. PARP is involved in various cellular processes related to DNA repair and programmed cell death. In DM, following glycolysis, the tricarboxylic acid cycle and polyol pathway are activated, which severely disturbs the ratio of nicotinamide adenine dinucleotide forms (NADH:NAD+), resulting in excessive NADH production and disruption of the redox balance[10]. Autoimmune stimulation triggers the infiltration of monocytes and macrophages into the pancreas, and free radicals and oxidants produced by monocytes and pancreatic cells, in combination, lead to intracellular DNA single-strand breaks and PARP activation. Moreover, depletion of cellular NAD+ leads to inhibition of cellular ATP production, resulting in cellular dysfunction and cell death. The marked loss of β cells decreases glucose tolerance and introduces hyperglycemia[11]. Hyperglycemia triggers the intracellular release of oxidative mediators from the mitochondrial electron transport chain, NADH/nicotinamide adenine dinucleotide phosphate hydrogen oxidases, and other sources, which then induce DNA single-strand breaks, thereby reactivating PARP. Furthermore, the effects of increased glucose levels are exacerbated by an increase in aldose reductase activity, leading to nicotinamide adenine dinucleotide phosphate hydrogen depletion and the production of reactive oxidants. PARP activation promotes the activation of activator protein 1, mitogen-activated protein kinases, and nuclear factor (NF)-κB, along with the expression of proinflammatory mediators, adhesion molecules, and inducible nitric oxide synthase (NOS)[12]. Ultimately, both PARP activation and mitochondrial oxidative stress form a positive feedback loop.

cGAS-STING in T2DM pathogenesis

Mitochondrial apoptotic pathway- and ER stress-induced lipotoxic injury in pancreatic β cells is an important pathological feature of T2DM[13]. The ER is the site of FFA esterification, and prolonged exposure to high-fat environments overloads its esterification capacity, leading to impaired ER function and enhanced ER stress. Intracellular oxidants affect mitochondria and lead to DNA single-strand breaks and cGAS-STING-IRF3 pathway activation[14]. Hu *et al*[15] reported that blocking the STING-IRF3 pathway ameliorated lipotoxicity-induced islet damage. Additionally, Wang *et al*[16] showed that the cGAS-STING pathway activated protein kinase B (Akt) to promote the inflammatory response. According to the studies, the specific mechanism is speculated as follows. Insulin regulates the production of glucose, lipids, and proteins through the phosphatidylinositol 3-kinase (PI3K) pathway. The substrate protein of the insulin receptor is phosphorylated, leading to the binding and activation of PI3K, which upregulates Akt, which is involved in insulin signaling, metabolism, cell growth, and cell cycle. Akt induces glucose transporter-4-mediated glucose transport into cells, promoting glucose metabolism in an insulin-dependent manner, and regulates the mammalian target of rapamycin (mTOR) *via* direct and indirect pathways. Reportedly, Akt phosphorylates mTOR and inhibits Ras homolog enriched in brain (Rheb) activation, a positive regulatory protein for mTOR activation, by inactivating tubulin sclerosis complex (TSC) 2 to enhance mTOR activation. Under normal circumstances, TSC-1 and TSC-2 form a dimeric complex that inhibits Rheb, thereby inhibiting the mTOR function. However, Akt can phosphorylate TSC-2 and inhibit the formation of the TSC-1/TSC-2 complex, thereby releasing the inhibitory effect on Rheb and activating mTOR[17]. Reportedly, mTOR mediates the association of Akt with the cGAS-STING pathway, and TBK1 can phosphorylate the S2159 site of mTOR to increase IFN-β levels[18]. TBK1 activation inhibits the activity of mTOR complex 1 (mTORC1)[19]. Altogether, these findings establish a relationship between the Akt protein family and the cGAS-STING pathway.

To explore the relationship between Akt and cGAS-STING pathway in DM pathogenesis, gene databases (www.genecards.org, https://omim.org/) were used, and "diabetes" and "cGAS-STING" were searched as keywords, which provided 18798 and 410 genes, respectively, along with 290 intersecting genes. Next, a protein-protein interaction network was formed using the STRING tool (version 11.5) to select the potential proteins in Akt-related pathways. The resulting data were imported into Cytoscape (version 3.9.1) for visualization (Figure 2A). The larger the circle area and the darker the color, the closer the association with other proteins. Figure 2B presents the 20 targets with the highest degree value. The higher the degree value, the closer the association with other proteins. Finally, the protein-protein interaction map was simplified, and TSC-1, TBK1, IRF3, and mTOR were found to be the interacting proteins between Akt-associated and cGAS-STING pathways (Figure 2C).

Table 1 Associations of the cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes pathway with diabetes and complications

Types of complications of diabetes	Link to cGAS-STING pathway	Ref.
Diabetic gastroenteropathy	Activation of PI3K/AKT/mTOR and AMPK/mTOR signaling pathways leads to apoptosis of gastric smooth muscle cells	Zhang *et al*[26]
	Phosphorylation of S2481 site on mTORC2 can promote glucose metabolism in gastrointestinal smooth muscle cells	Yan *et al*[27]
	cGAS STING regulates mTORC1 mediated cell apoptosis through TBK1 signaling	Bodur *et al*[28]
	cGAS STING regulates mTORC1 mediated cell apoptosis through TREX1 signaling	Hasan *et al*[29]
	cGAS/STING/IRF3/NF-κB/INF pathway participates in mitochondrial autophagy in the stomach and duodenum	Puthanmadhom Narayanan *et al*[32]
Nonalcoholic fatty liver disease	Activation of the STING signaling pathway enhances hepatic steatosis and inflammatory response, exacerbating hepatic stellate cell fibrosis	Wang *et al*[48], Yu *et al*[49]
	STING promotes macrophage induced liver cell fat deposition and pro-inflammatory response through the NFB and JNK pathways	Luo *et al*[47]
	STING and IRF3 activation promote lipid accumulation in stem cells	Qiao *et al*[50]
	Mitochondrial autophagy mediated mtDNA/cGAS/STING signaling plays a broad regulatory mechanism in different aseptic inflammatory responses	Su *et al*[51]
	Pink1 can inhibit cGAS/STING activation and reduce mitochondrial autophagy	Zhong *et al*[52]
Diabetic cardiomyopathy	The use of STING inhibitors in both the lipotoxic H9C2 cell model and the DCM mouse model can significantly inhibit myocardial cell inflammation and apoptosis	Ma *et al*[54]
	cGAS/STING pathway initiates NLRP3 inflammasome induced cardiomyocyte pyroptosis and chronic inflammation	Yan *et al*[55]
	cGAS/STING signaling activates the autophagy pathway LKB1/AMPK/ULK1 in cardiomyocytes, leading to hypertrophy, apoptosis, and oxidative damage in primary neonatal rat cardiomyocytes. The cardiac specific overexpression of Metrnl can improve the cardiac injury in diabetes mice	Lu *et al*[56]
	MtDNA activates the cGAS STING pathway, promoting epithelial mesenchymal transition in vascular endothelium	Liu *et al*[58]
	cGAS exacerbates the inflammatory cascade and participates in the formation of atherosclerosis through the synergistic signaling of IRF and IFN	Lu *et al*[59], Pham *et al*[60]
	TDP43 serves as an upstream regulatory factor in AS, triggering inflammatory responses by inducing the release of mtDNA and activating the cGAS STING pathway	Huangfu *et al*[61]
Diabetes nephropathy	The cGAS STING signaling pathway of renal macrophages is activated, and macrophages are activated towards M1 type through NF-κB signaling protein leads to TNF-α and IL-1β release increase	Han *et al*[67]
	Damage to autophagy in podocytes leads to the accumulation of damaged mitochondria, and TBK1 is an important downstream molecule of the cGAS-STING pathway in podocytes	Zang[68], Myakala *et al*[69]
	Sacubitril/valsartan can repair mtDNA damage, inhibit cGAS/STING pathway activation, and protect renal function	Myakala *et al*[70]
	DsbA-L can antagonize cGAS/STING pathway activation and improve high glucose induced renal tubular injury	Yang *et al*[71]
Diabetic retinopathy	The levels of STING and p-TBK1 protein in retinal endothelial cells of diabetes mice were significantly increased	Wen *et al*[74]
	STING influences PPAR by α plays a key role in the degeneration of retinal glial cells and vascular damage	Yuan *et al*[75], Dong *et al*[79]
	TGR5 blocks the IP3R1-GRP75-VDAC1 axis mediated efflux of Ca^{2+} from the endoplasmic reticulum to mitochondria	Li *et al*[76]
	Upregulation of *ARPE-19* gene expression and STIGN-NF-κB pathway	Chen *et al*[77]

	activation related	
	JQ-1cGAS-STING inhibitor can alleviate retinopathy caused by oxidative stress in diabetes	Zou *et al*[78]
Diabetic wound	ROS induces macrophage polarization through mtDNA/STING signaling, exacerbating endothelial cell dysfunction	Geng *et al*[81]
	STING inhibitors can inhibit inflammation and promote wound healing	Feng *et al*[82]
	IRF3 regulates Hippo YAP pathway to inhibit wound healing	Yuan *et al*[83]
	STING leads to an increase in JMJD3 in macrophages, limiting wound repair and enhancing inflammatory response	Audu *et al*[84]

cGAS: Cyclic guanosine monophosphate-adenosine monophosphate synthase; STING: Stimulator of interferon gene; PI3K: Phosphatidylinositol 3-kinase; AKT: Activated protein kinase B; mTOR: Mammalian target of rapamycin; mTORC2: Mammalian target of rapamycin complex 2; TBK1: TANK-binding kinase 1; TREX1: 3-prime repair exonuclease 1; IRF3: Interferon regulatory factor 3; NF-κB: Nuclear factor-κB; IFN: Interferon; JNK: c-Jun NH2-terminal kinase; mtDNA: Mitochondrial DNA; NLRP3: Nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing protein 3; Metrnl: Meteorin-like; AS: Atherosclerosis; TNF: Tumor necrosis factor; IL: Interleukin; PPAR: Peroxisome proliferator-activated receptor; TGR5: Takeda G protein-coupled receptor 5; ROS: Reactive oxygen species; YAP: Yes-associated protein; JMJD3: Jumonji domain-containing protein-3.

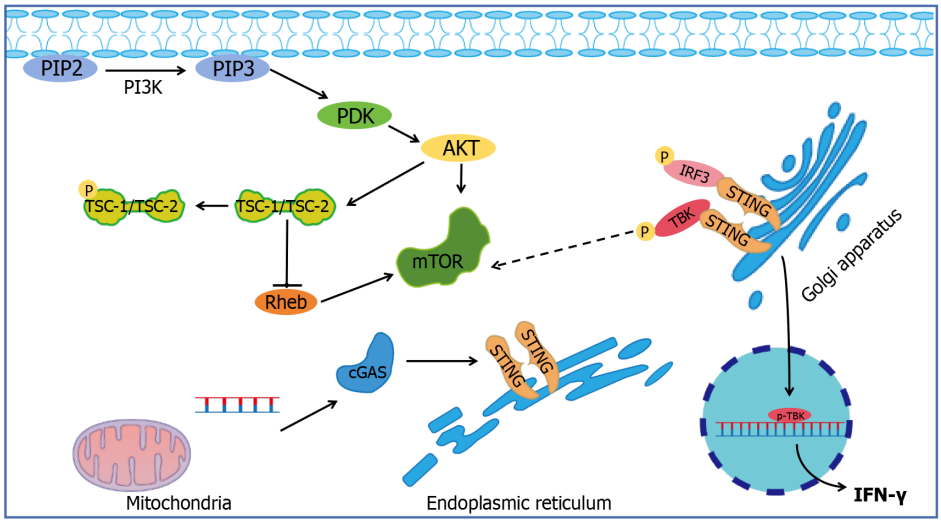
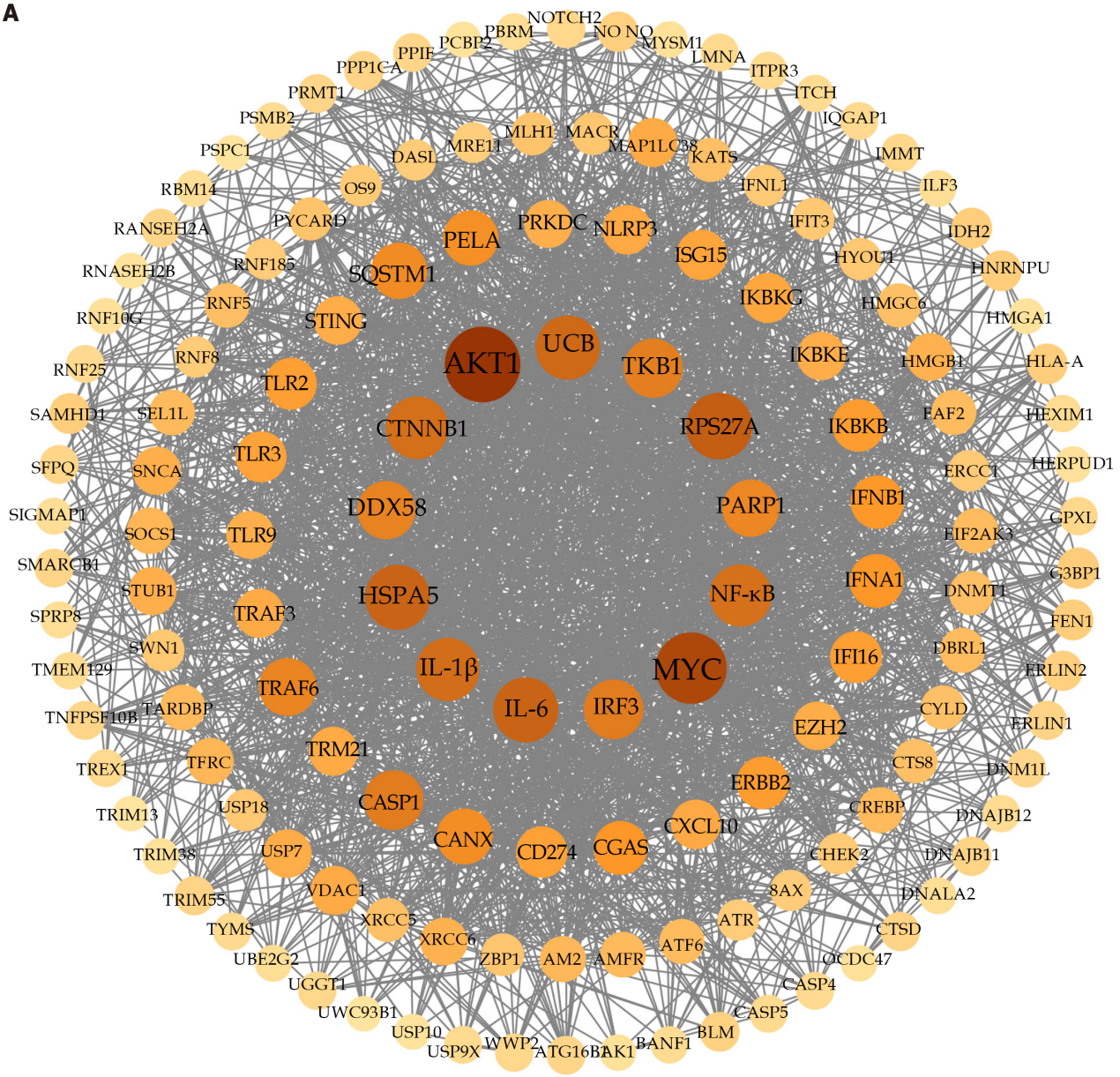


Figure 1 The binding of cyclic guanosine monophosphate-adenosine monophosphate synthase to double-stranded DNA results in its activation as a secondary messenger, leading to the production of cyclic guanosine monophosphate-adenosine monophosphate. Cyclic guanosine monophosphate-adenosine monophosphate then binds to interferon gene stimulating factor (STING), which is bound to the endoplasmic reticulum (ER) membrane, thereby causing its activation. STING conformational change and transfer to the Golgi apparatus. In the Golgi apparatus, the two cysteine residues of STING (Cys88 and Cys91) are palmitoylated. Subsequently, STING will recruit TANK binding kinase 1 (TBK1) and interact with it. TBK1 phosphorylates interferon regulatory factor 3 (IRF3), triggering dimerization, nuclear translocation, and induction of target genes in IRF3, thereby affecting interferon production. Activated protein kinase B can directly phosphorylate mammalian target of rapamycin (mTOR); or inhibit the activation of Ras homolog enriched in brain by inactivating tuberous sclerosis complex 2, and then enhance the activation of mTOR. TBK1 increase the activation of mTOR, on the contrary, phosphorylation of TBK1 inhibits the activity of mTOR. PIP2: Phosphatidylinositol-(3,4)-P2; PIP3: Phosphatidylinositol-(3,4,5)-P3; PI3K: Phosphatidylinositol 3-kinase; PDK: Phosphoinositide-dependent kinase; mTOR: Mammalian target of rapamycin; cGAS: Cyclic guanosine monophosphate-adenosine monophosphate synthase; STING: Stimulator of interferon gene; TSC: Tuberous sclerosis complex; Akt: Activated protein kinase B; TBK: TANK binding kinase; IRF: Interferon regulatory factor 3; IFN: Interferon; Rheb: Ras homolog enriched in brain.

CGAS-STING IN DG PATHOGENESIS

DG includes all gastrointestinal manifestations of DM. Reportedly, up to 50% of patients with T1DM, T2DM, or poor glycaemic control exhibit delayed gastric emptying (GE)[20]. Owing to poor understanding of the disease by clinicians and unclear early symptoms, DG is often misdiagnosed. Scintigraphy or capsule magnetic resonance endoscopy is the main diagnostic approaches for DG. Many patients can present with gastroparesis, a characteristic syndrome of moderate-to-severe upper gastrointestinal symptoms, or delayed gastroparesis, but without gastric outlet obstruction. Gastroparesis can significantly affect the quality of life, with up to 50% of patients experiencing severe symptoms of anxiety or depression. Diabetic gastroparesis is generally used to describe the upper gastrointestinal manifestations of DM, but not all gastrointestinal symptoms originate from the stomach, some also originate from the small intestine[21]. Therefore, DG is used, as a broader term, to describe all the gastrointestinal manifestations of DM including gastroparesis and diabetic dyspepsia. Diabetic dyspepsia is characterized by upper gastrointestinal symptoms, along with normal,

A



B

No.	Protein	Degree	No.	Protein	Degree
1	AKT1	93	11	mTOR	60
2	MYC	84	12	TBK1	59
3	RPS27A	74	13	DDX58	57
4	HSPA5	71	14	TRAF6	56
5	IL6	71	15	PARP1	55
6	UBC	69	16	SQSTM1	53
7	IL1B	67	17	CASP1	52
8	CTNNB1	66	18	RELA	51
9	NFKB1	65	19	CGAS	48
10	IRF3	60	20	IFNA1	48

C

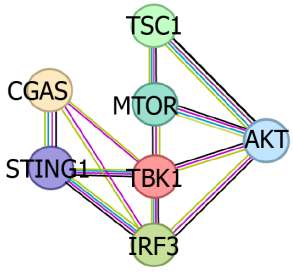


Figure 2 Gene database-based target analysis of the cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes pathway in diabetes mellitus. A: Combination between "diabetes" and "cGAS-STING" predicted by String database (version 11.5); B: The 20 targets with the highest degree value; C: The protein interaction diagram of the interaction between "Akt" and "cGAS-STING". mTOR: Mammalian target of rapamycin; cGAS: Cyclic guanosine monophosphate-adenosine monophosphate synthase; STING: Stimulator of interferon gene; TSC: Tuberous sclerosis complex; Akt: Activated protein kinase B; TBK: TANK binding kinase; IRF: Interferon regulatory factor 3; IFN: Interferon; IL: Interleukin; NF-κB: Nuclear factor-κB; PARP: Polyadenosine diphosphate-ribose polymer.

mild, or asymptomatic delayed GE. The latter accounts for 40% of patients with DM and delayed GE[22]. The main symptoms of diabetic gastroparesis include postprandial satiety, nausea, vomiting, abdominal distension, epigastric pain, and weight loss. In T2DM, the age at which symptoms appear is later than that in people with T1DM or idiopathic gastroparesis. Approximately 14% of people with both T1DM and T2DM present symptoms of infection before they become ill. Furthermore, approximately 33% of patients with idiopathic and diabetic gastroparesis present intermittent worsening of symptoms[23].

In recent years, diabetes gastroparesis has been related to many factors, including disorders of autonomic nervous structure and function (sympathetic and parasympathetic imbalance), intestinal neuromuscular dysfunction, and glucose and hormone metabolism disorders. These pathological and physiological changes can lead to abnormal gastric electrophysiology and gastrointestinal sensory, as well as motor dysfunction. The gastrointestinal nervous system contains approximately 100 million neurons, which are organized into different ganglia, including movement-regulating intermuscular plexus, and absorption- and secretion-regulating submucosal plexus[24]. The interstitial cells of Cajal (ICC) play a role in the pacemaker and information transmission. In patients with DM and laboratory diabetic rats, cells in the motor vagus nerve and sympathetic ganglion have been reported to reduce, and structural changes such as segmental demyelination and axonal degeneration have been observed in vagus nerve fibers in the myenteric plexus, submucosal plexus, and outside of the gastrointestinal tract. The loss of nerve fibers is usually multifocal, indicating ischaemic injury. Mainly, a decrease in intestinal neurons or ICC induces dysfunction of the intestinal neuromuscular function. Consequently, the number of macrophages associated with immune macrophage inhibitory neurons and neuronal NOS expression decreases. Studies have shown that the interaction between macrophages, ICC, and neuromuscular cells may play an important role in DM-induced gastroparesis. Alternating M2 macrophages that express cytoprotective markers such as hem oxygenase-1 have been reported in the gastric mucosal layer of normal mice. In mice with delayed GE, the intrinsic macrophages predominantly comprise classically activated M1 macrophages that produce cytokines inducing ICC apoptosis[25].

cGAS-STING and autophagy mechanism in diabetic cells

ICC apoptosis in the gastrointestinal tract is one of the pathogenic mechanisms of gastroparesis. Studies have reported the involvement of two mTOR, a protein kinase associated with apoptosis, energy metabolism, and DM, pathways in ICC apoptosis, namely the PI3K/Akt/mTOR inhibitory apoptotic pathway and the adenosine monophosphate-activated protein kinase (AMPK)/mTOR pro-apoptotic pathway. In early diabetic gastroparesis, ICC increases growth factor secretion upstream of the PI3K/Akt pathway by autocrine or paracrine mechanisms in response to an initial high glucose (HG) stimulus, activating the anti-apoptotic effects to maintain cell function. Continuous and prolonged hyperglycemic stimuli result in the inhibition of the apoptotic pathway, which is difficult to compensate for. At this point, the pro-apoptotic AMPK/mTOR pathway becomes dominant. AMPK phosphorylates and activates TSC-2 upstream of mTOR, promoting TSC-1/TSC-2 complex formation, decreasing mTOR activity, and thus, leading to ICC apoptosis[26]. Yan *et al*[27] found that phosphorylating the S2481 site on mTORC2 can promote glucose uptake, glucose metabolism, and ATP synthesis in the gastrointestinal smooth muscle. Furthermore, Bodur *et al*[28] showed that the innate immune kinase TBK1 regulates anti-inflammatory effects by stimulating type I IFN (IFN-I) production. TBK1 directly activates mTORC1 in the cells through specific mTOR phosphorylation (S2159 phosphorylation site), revealing the stimulus-selective role of TBK1 in mTORC1 regulation. A study on macrophages isolated from genome-edited mTOR S2159A-knockout mice revealed that mTOR S2159 phosphorylation promoted mTORC1 signaling, IRF3 nuclear translocation, and IFN-β production, indicating a mechanistic link between the cGAS-STING-TBK1 signaling pathway and the mTORC1 function in cell apoptosis. Hasan *et al*[29] found that 3-prime repair exonuclease 1 (TREX1), which exhibits DNA enzyme activity, can sense cytoplasmic DNA and activate IFN responses through the cGAS-STING pathway. The significant decrease in the mTORC1 activity in TREX1-/- mouse tissues suggested that the cGAS-STING pathway may play an important role in mTORC1 regulation and metabolism. These findings suggest the cGAS signaling pathway as a new target for the treatment of gastrointestinal neurological function; however, further research is needed to fully elucidate the complex cGAS-STING signaling-gastrointestinal neuromodulation interplay.

cGAS-STING and macrophages in DM and polarization mechanism

The intestinal neuronal apoptosis is associated with ICC and macrophages, and neuronal NOS-expressing neurons are the first to be eliminated. Reportedly, the interactions among macrophages, ICC, and the neuromuscular system may mediate gastroparesis in mice and humans with DM. The muscular layer of the gastric mucosa of normal GE mice is filled with alternatively activated M2 macrophages that express cytoprotective markers, including hem oxygenase-1. In mice with delayed GE, classically activated M1 macrophages are predominant and produce cytokines leading to ICC apoptosis. Macrophages are necessary for the development of delayed GE in diabetic mice[30]. Deng *et al*[31] reported that high-fat diet (HFD)-induced aseptic neuritis is related to the polarization of astrocytes and M1 microglia. Microglia are macrophage-like cells in the central nervous system, and their aggregation can be symptomatic of neurodegenerative diseases such as Alzheimer's and Parkinson's, which can cause GE disorders in the gastrointestinal tract. A HFD can damage mitochondrial DNA (mtDNA) in the stomach and duodenum through oxidative stress[32]. High blood glucose increases pyruvate production, leading to mitochondrial membrane hyperpolarization and free radical production, which then oxidatively damage susceptible mtDNA with limited repair capacity. This damage increases mitochondrial autophagy, and as both mtDNA and nuclear DNA in cells can activate the cGAS-STING-IRF3-NF-κB-INF pathway, chronic neuroinflammatory responses are triggered. Although the mechanism of cGAS-STING signaling in the gastrointestinal nervous system remains unelucidated, its important role in central chronic neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and ischaemic brain injury is well known[33]. Overall, these findings suggest the potential of cGAS as a target for glial cell polarization and cGAS-STING as a potential

therapeutic target in the gastrointestinal nervous system, warranting further research.

cGAS-STING and the mechanism of gut microbiota dysbiosis

Dysbiosis is both a cause and a consequence of gastrointestinal dysfunction in DM. The gastrointestinal tract is exposed to microorganisms, and hence, is an important defense barrier for the body. In the classical pathway, IFN-I play a crucial role in intestinal defense and is associated with intestinal immune dysfunction. The cGAS-STING signaling pathway induces IFN-I in the presence of exogenous DNA and plays a crucial role in gastrointestinal homeostasis[34]. In the intestinal mucosa, mainly dendritic cells and monocytes located in the lamina propria release IFN-I during homeostasis. Similar findings have been observed in both mouse and human intestines, where IFN-I directly bound STING to bacterial cyclic dinucleotides, which act as secondary messengers in bacteria, establishing STING as an independent pattern recognition receptor. The gut microbiota maintains IFN-I signaling and is critical for the immune recognition of dendritic cells[35]. The absence of STING is associated with a higher susceptibility to inflammation in the gut microbiota. In non-classical pathways, STING binds to nuclear transcription factors. In 2020, Obata *et al*[36] reported the biosensor activity of aromatic hydrocarbon receptor (AHR) in the intestinal neural network and the close association of its functional expression to the gut microbiota in regulating the excitability of intestinal neurons and intestinal physiological functions. In 2023, Zhang *et al*[37] showed that AHR activation is driven by STING1, a nuclear protein, and it controls the composition of intestinal microflora, but this function was not dependent on DNA sensing and autophagy and competed with cGAS-STING signaling inhibition. They compared the differences between wild-type and STING1Gt/Gt mice (lack of functional STING1 expression). STING1 knockout attenuated the protective effects of AHR ligands on gut microbiota and innate immunity. Nuclear STING1 exhibits various independent functions of IFN, which are essential for regulating intestinal immunity and microbial homeostasis. Collectively, these findings suggest that STING-mediated microbial signaling is critical in the surveillance of gut microbiota and that STING overexpression leads to disease progression and tissue dysfunction *via* IFN-I[38].

Extracellular vesicles (EVs) can transport various biomolecules, including RNA, DNA, proteins, and lipids, within living organisms[39]. Disrupted gut barrier in patients with DM results in the leakage of microbiota-derived products into the circulatory system of the host, and thus, in distant organs. In diabetic mice, gut microbiota-derived EVs encasing microbial DNA were shown to be captured by pancreatic CD11c+ islets, subsequently initiating a cellular inflammatory response *via* the cGAS-STING signaling pathway, which promoted pancreatic islet inflammation and β cell abnormalities [40]. In the liver, cGAS-STING activation following the capture of EVs by Vsig4+ macrophages has been shown to exacerbate the development of NAFLD and liver fibrosis[41]. Additionally, Enterobacteriaceae fragilis EVs can promote macrophage M1/M2 polarization and induce vascular complications in individuals with T2DM[42]. Although validated in animal models, the efficacy of EV-mediated cGAS-related signaling pathway activation remains unelucidated in humans. The cGAS-STING pathway recognizes bacterial cyclic dinucleotides, sustains the growth of probiotics, and maintains gut homeostasis[43]. Decreased probiotic populations can cause immune dysregulation in the host, increasing the risk of pathogenic invasion. Lactobacillus, the major probiotic genus in the gut, stimulates IFN-I expression through the cGAS-STING pathway and induces macrophage-specific immune responses. Reportedly, STING can promote the production of short-chain fatty acids by utilizing intestinal bacteria and induce mucosal immunity in a G-protein coupled receptor 43-dependent manner, which reduces bacterial translocation by preserving the integrity of the intestinal barrier [44]. Overall, the interaction of intestinal probiotics with the cGAS-STING pathway facilitates the maintenance of intestinal homeostasis, whereas STING deficiency can increase intestinal susceptibility to inflammation and alterations in the intestinal flora.

CGAS-STING IN NAFLD PATHOGENESIS

NAFLD, a clinical-pathological syndrome, refers to the accumulation of excessive fat in liver cells because of factors other than alcohol consumption, including simple fatty liver, non-alcoholic steatohepatitis (NASH), liver cirrhosis, and hepatocellular carcinoma. DM-driven dyslipidemia, inflammatory response, IR, and other mechanisms affect the progression of NAFLD. Approximately 75% of patients with T2DM have NAFLD[45].

NAFLD pathogenesis has been related to innate immune-mediated aseptic inflammation, and IFN-I has played an important role in its development[46]. Luo *et al*[47] reported that cGAS, STING, and IRF3 levels were increased in the liver of NAFLD or NASH mice and activated the pro-inflammatory response of liver macrophages. They investigated the role of STING in NAFLD using wild-type C57BL/6J mice fed with HFD and a low-fat diet for 12 weeks. STING knockout inhibited the production of several inflammatory cytokines induced by HFD. The experimental results showed that D played a detrimental role. Furthermore, the macrophage liver cell co-culture experiment showed that STING promoted macrophage-induced fat deposition and pro-inflammatory response in liver cells through the NF-κB and Jun N-terminal kinase pathways.

Wang *et al*[48] showed the crucial role of STING in NAFLD progression based on the analyses of liver samples from 98 patients with NAFLD and 8 controls. STING and phosphorylated TBK1 (p-TBK1) expression in non-parenchymal liver cells increases with the severity of inflammation and fibrosis, particularly in hepatic portal vein macrophages of patients with fibrotic NASH. Activation of the STING pathway in macrophages enhances hepatic steatosis and inflammatory response, thereby exacerbating hepatic stellate cell fibrosis. These findings suggest the involvement of the cGAS-STING pathway in NAFLD or NASH pathogenesis. Yu *et al*[49] reported an increase in mtDNA in liver cells of mice fed with a methionine- and choline-deficient diet and an HFD; furthermore, the STING signaling pathway was induced in cultured Kupffer cells. Notably, STING deficiency alleviated hepatic steatosis, fibrosis, and inflammation in the NASH mouse

model, along with serum cholesterol, triglyceride, and low-density lipoprotein low-density lipoprotein (LDL) levels. Qiao *et al*[50] reported upregulated STING and IRF3 in the liver of HFD-fed mice and FFA-induced L-O2 liver cells by regulating NF-κB signaling pathways, inflammatory cytokines, and apoptotic signaling pathways, which increase fat deposition. STING or IRF3 knockdown significantly reduces FFA-induced liver inflammation, lipid accumulation, and cell apoptosis, and increases glycogen storage, which is associated with reduced expression of gluconeogenesis- and lipid synthesis-associated liver enzymes. Su *et al*[51] found that mitochondrial autophagy-mediated mtDNA/cGAS/STING signaling plays a broad regulatory mechanism in various aseptic inflammatory responses and macrophage STING signaling notably promoted aseptic inflammatory liver injury in aged mice. STING knockout in liver injury models can significantly alleviate liver injury in aged mice. Analyses of the STING/TBK1 signaling pathway, *TNF-α*, and *IL-6* gene showed that STING knockout ameliorated the age-dependent increase in the pro-inflammatory response of the liver. This suggests that STING deficiency may protect older mice from various types of sterile inflammatory liver injury. Zhong *et al*[52] reported similar observations and confirmed that aging damages macrophage mitochondria, leading to the activation of mitochondrial autophagy. Phosphatase and tensin homolog deleted on chromosome ten-induced kinase 1 overexpression and Torin1 treatment can restore mitochondrial autophagy and inhibit cGAS-STING activation in aging macrophages.

CGAS-STING IN DCM PATHOGENESIS

DCM is a serious cardiac complication of DM that can lead to heart failure even without valvular disease, hypertension, and coronary artery disease. Risk factors for coronary heart disease in DM are high blood glucose, blood pressure, cholesterol, and LDL levels, along with decreased high-density lipoprotein, age, sex, smoking, and family history. DM negatively affects the heart, leading to changes in gene expression, abnormal energy metabolism, reduced left ventricular function, oxidative stress, aseptic inflammation, lipid accumulation, and mitochondrial dysfunction, which can result in the onset and development of cardiac dysfunction, myocardial hypertrophy, and myocardial remodeling[53]. The clinical symptoms of DCM include heart failure, angina pectoris, and arrhythmia among other symptoms, which is the greatest risk factor for death in patients with diabetes. Presently, there are no specific treatments for DCM. In recent years, research on DCM pathogenesis has gradually increased, suggesting an association with the cGAS-STING pathway.

Ma *et al*[54] reported that in HFD-fed T2DM mice, mtDNA in the cytoplasm of mouse cardiomyocytes increased and the cGAS-STING pathway was activated, along with the increased expression of downstream molecules IRF3, NF-κB, IL-18, and IL-1β. Further validation using palmitic acid (PA) to cultivate H9C2 in lipophilic rat cardiomyocytes showed that the intracellular cGAS-STING pathway was activated, resulting in an increase in cytoplasmic mtDNA. PA induced changes in mitochondrial homeostasis, resulting in an excessive production of mitochondrial reactive oxygen species and oxidative damage to mtDNA. STING inhibitors significantly inhibited myocardial cell inflammation and apoptosis in both lipid-toxic H9C2 cell models and DCM mouse models. Yan *et al*[55] induced DM in STING-knockout mice by injecting streptozotocin (STZ) and HFD and found that STING knockout reduced myocardial cell scorch and inflammatory response, preventing DM-induced cardiac hypertrophy and improving cardiac function. Mitochondrial oxidative damage and FFAs induce mtDNA escape, stimulating the cGAS-STING pathway to initiate nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing protein 3 (NLRP3) inflammasome-induced cardiomyocyte pyroptosis and chronic inflammation. In hyperlipidemia or hyperglycemia, mitochondrial dysfunction is the main reason for the increase in mtDNA. These findings suggest the importance of the mtDNA-activated cGAS-STING pathway in the pathogenesis of DCM and that STING is a potential target for treating DCM. Meteorin-like (Metrnl) is an important secretory adipocyte factor discovered recently and plays an important role in regulating glycolipid metabolic diseases such as dyslipidemia, obesity, T2DM, coronary heart disease, and NAFLD. Lu *et al*[56] found that plasma Metrnl, myocardial Metrnl protein, and mRNA levels were significantly downregulated in STZ-induced T1DM and leptin receptor-deficient (db/db) T2DM mice. cGAS-STING signaling activates the liver kinase B1/AMPK/Unc-51-like kinase 1 autophagy pathway in cardiomyocytes, leading to hypertrophy, apoptosis, and oxidative damage in primary neonatal rat cardiomyocytes. Overall, cardiac-specific overexpression of Metrnl can ameliorate cardiac injury and dysfunction in T1DM and T2DM mice.

MACROVASCULAR LESION AND VASCULAR ENDOTHELIAL INJURY IN DM

cGAS-STING contributes to both macrovascular and microvascular complications in DM, with major risk factors including long duration of DM, poor glycemic control, hypertension, hyperlipidemia, and IR. DM-induced vascular atherosclerosis is the basis of coronary heart disease, cerebrovascular disease, and peripheral arterial disease in DM. Additionally, the combination of these diseases and other cardiovascular events caused by atherosclerosis is collectively referred to as atherosclerotic cardiovascular disease, which is responsible for the death of approximately 45% of patients with DM[57]. The cGAS-STING-mediated inflammatory response mainly involves LDL accumulation in the vascular intima, activating the expression of leukocyte adhesion molecules and chemokines in endothelial cells, promoting the recruitment of macrophages and T cells, and promoting local inflammation and plaque growth by secreting pro-inflammatory cytokines. Liu *et al*[58] exposed human aortic endothelial cells to different concentrations of PA. Notably, the cGAS-STING pathway was selectively activated by mtDNA and promoted epithelial-mesenchymal transition in vascular endothelium. cGAS knockdown attenuated PA-induced activities, suggesting the involvement of the mtDNA-induced cGAS-STING pathway in endothelial dysfunction. Reportedly, mtDNA triggers primary autoimmune activation by

evading self-clearance (DNA degradation and autophagy), thereby exacerbating the formation of atherosclerosis lesions. Lu *et al*[59] reported that cGAS exacerbates the inflammatory cascade through the synergistic signaling of IRF and IFN, triggering the transformation of macrophage phenotype to M1 (pro-inflammatory phenotype) and increasing lipid deposition by upregulating the uptake of cholesterol-related molecules, thereby leading to atherosclerosis. Pham *et al*[60] found that the STING pathway promotes atherosclerosis through pro-inflammatory activation of macrophages. They found that lipids and macrophages accumulated in atherosclerotic plaques of the mouse aorta, and the expression of STING, cGAMP, and IFN-I in macrophages was increased. Furthermore, in STING-knockdown mice, atherosclerosis lesions in the aortic arch, lipid and macrophage accumulation in plaques, and expression of inflammatory molecules in the aorta were reduced. Huang *et al*[61] showed that the transactive response DNA binding protein of 43 acts as an upstream regulator in atherosclerosis, activating the cGAS-STING pathway by inducing the release of mtDNA and triggering inflammatory responses. Increasing evidence suggests a close association between NLRP3 inflammasomes and atherosclerosis, warranting the investigation of the role of NLRP3 inflammasome regulation and activation mechanisms in atherosclerosis. Altogether, these studies show that cGAS-STING-mediated inflammatory response plays an important role in developing diabetic macroangiopathy, suggesting a new direction for research on treatment.

CGAS-STING IN DNE PATHOGENESIS

DNe is a microvascular complication characterized by the deterioration of renal function. Despite strict blood pressure control, approximately 40% of patients with DM develop DNe because of the use of statins and renin-angiotensin system inhibitors. The main symptoms include overall renal dysfunction, thickening of the glomerular basement membrane, reduction of podocytes in the glomerulus, expansion of mesangial volume, nodular lesions, and proliferation of hyaline substance[62]. Owing to the death of numerous glomeruli, the glomerular filtration rate and the production of large amounts of proteinuria decreases, ultimately leading to total renal failure. Inflammation plays an important role in the pathogenesis of podocyte injury. Saito *et al*[63] found that TNF-α could reduce the expression of the podocyte structural protein nephrin. Pedigo *et al*[64] reported that TNF-α could inhibit podocyte cholesterol efflux, leading to cholesterol accumulation and podocyte apoptosis. Gutwein *et al*[65] showed that TNF-α and IFN-γ induced CXC chemokine ligand 16 expression in podocytes, ultimately disrupting the lipid metabolism in podocytes. Herder *et al*[66] found that IL-6 could increase signal transducer and activator of transcription 3 expression leading to fusion and disappearance of foot processes in podocytes. The cGAS-STING pathway plays an important role in mediating metabolic inflammation. Reportedly, the cGAS-STING pathway is involved in DNe pathogenesis. In an HG environment, mature macrophages are activated into M1 macrophages, leading to chronic kidney inflammation. Han *et al*[67] found that numerous CD86+ M1 macrophages infiltrated the kidney tissue of patients with DNe, and STING expression was significantly increased, indicating the upregulation of the cGAS-STING pathway. Mouse macrophage RAW264.7 *in vitro* analysis under HG stimulation showed activation of the macrophage cGAS-STING signaling pathway, transformation to the M1 type, phosphorylated p65 and NF-κB upregulation, and increased release of TNF-α and IL-1β. The addition of STING inhibitor C-176 markedly inhibited the activation of M1 macrophages and the expression of downstream inflammatory proteins and cytokines. These findings confirm the activation of the macrophage cGAS-STING signaling pathway under HG conditions. Zang[68] used a podocyte line PA injury model of db/db mice and MPC5 mice as a model of DNe. The renal pathology showed a hypertrophic glomerulus, slightly dilated mesangium, reduced expression of the podocyte marker protein nephrin, widely fused podocytes, irregularly thickened glomerular basement membrane, and increased levels of podocyte apoptosis. Activation of the cGAS-STING pathway was detected mainly in renal cortical podocytes, with increased cGAS and STING expression, and increased TBKI phosphorylation, but unchanged levels of IRF3 phosphorylation and IFN-β. The protective effect of C-176 or STING knockout in damaged lipotoxic podocytes is exhibited through cellular autonomy, consistent with animal experiments. The mode of activation of the cGAS-STING pathway in MPC5 cells was through STING-TBK1-p65-IRF3 was not activated-consistent with animal experiments. GSK8612 inhibition of TBK1 is sufficient to induce cellular self-protection, suggesting that TBK1 is an important downstream molecule of the cGAS-STING pathway in podocytes. Damage to podocyte autophagy leads to the accumulation of damaged mitochondria, and mtDNA leaks into the cytoplasm through Bcl-2 associated X-protein-mediated macropores, activating the cGAS-STING/TBK1/p65 pathway, thus, resulting in the production of inflammatory factors and podocyte damage. Myakala *et al*[69] reported that cGAS activation induces nephritis in db/db and KKAy mice. DNA damage or mitochondrial dysfunction can release DNA into the cytoplasm to activate cGAS, leading to the production of the second messenger cGAMP. Subsequently, STING induces the IFN-I response or NF-κB activation, thereby inducing the expression of inflammatory factors. Myakala *et al*[70] reported that sakubatrox/valsartan can repair mtDNA damage, inhibit the activation of the cGAS-STING pathway, and reduce proteinuria, mesangial dilation, and podocyte loss in db/db and KKAy mice, and thus, exhibit a protective effect on renal function in T2DM mice. Disulfide bond-forming oxidoreductase A-like protein overexpression can antagonize mitochondrial stress-induced mtDNA release and activation of the cGAS-STING pathway in adipose tissue, ameliorate HG-induced renal tubular injury, and prevent ectopic fat deposition and lipid-related kidney injury in DNe[71]. Additionally, mitochondrial dysfunction and tubular inflammation contribute to the pathogenesis of acute kidney injury and subsequent chronic kidney disease. Reportedly, activating the cGAS-STING pathway in the kidneys of patients with acute kidney injury resulted in cisplatin-induced tubular inflammation, whereas STING knockout ameliorated the acute kidney injury phenotype. Furthermore, inhibition of STING can alleviate folate-induced nephritis, tubular injury, renal fibrosis, and mitochondrial dysfunction in mice. Altogether, activation of the cGAS-STING pathway can lead to kidney injury, whereas its inhibition can delay the progression of kidney diseases.

CGAS-STING IN DR PATHOGENESIS

DR is a microvascular complication of DM. Currently, 8 out of the world's adult population have DM. 5% of the adult population have DM, and approximately 30% of patients with DM can develop DR[72]. DR is one of the retinal inflammatory diseases that can lead to loss of tight junctions, increased permeability, thickening of the basement membrane, and loss of peripheral cells in the retina. Hyperglycemia can affect normal glucose metabolism *via* the polyol pathway, hexosamine pathway, advanced glycation end products, and protein kinase C[73], leading to oxidative stress, cytokine release, mitochondrial dysfunction, and immune system activation. Therefore, targeting cGAS and STING expression in various retinal cell types may be a potential therapeutic approach for DR.

Wen *et al*[74] reported significantly increased levels of STING and p-TBK1 in retinal endothelial cells of HFD-fed diabetic mice. *In vitro*, PA treatment can induce mtDNA leakage into the cytoplasm of human retinal vascular endothelial cells and increase p-TBK1 protein and *IFN-β* mRNA levels. The STING pathway alleviates endothelial inflammation and provides an optional therapeutic target for treating DR and other microvascular complications of DM. Yuan *et al*[75] showed that the STING pathway was activated in DR by affecting PPARs in glial cells cultured with diabetes Prara-/- mice and diabetic stressor 4-hydroxynonenal cytokines. Glucose metabolism in retinal glial cells plays a crucial role in microglioma, neurodegeneration, and vascular damage. Li *et al*[76] reported that mitochondrial Ca^{2+} overload led to the opening of mitochondrial permeability transition pores and mtDNA leakage into the cytoplasm in rats, activating cytoplasmic mtDNA, cGAS, and stim-mediated inflammatory responses. Takeda G protein-coupled receptor 5 agonists can alleviate mitochondrial Ca^{2+} overload and mitochondrial dysfunction. Takeda G protein-coupled receptor 5 blocks the efflux of Ca^{2+} from the ER to the mitochondria, which is mediated by the inositol 1,4,5-triphosphate receptor-75-kDA glucose-regulated protein-voltage-dependent anion channel 1 axis. Chen *et al*[77] found that the adult retinal pigment epithelial cell line-19 gene was upregulated in oxidative stress-induced retinal aging, and vascular endothelial growth factor and its key mediator hypoxia-inducible factor-1 was involved. The expression of STING was increased, and the specific mechanism may be related to DNA clearance disorders and STING-NF-κB pathway activation. Similarly, Zou *et al*[78] used JQ-1cGAS-STING inhibitor to ameliorate oxidative stress-induced DR. Dong *et al*[79] reported that monocyte activation plays an important role in DR and other DM complications. PPARα is significantly downregulated in monocytes derived from animals and patients with DM, impairing mitochondrial function, increasing monocyte glycolysis, increasing mtDNA release in the cytoplasm of diabetic monocytes, and activating the cGAS-STING pathway. Notably, STING knockout or STING inhibitor can attenuate DM or PPARα knockout-induced monocyte activation.

CGAS-STING IN DW PATHOGENESIS

DW is a chronic complication that affects wound closure in patients with DM. DW pathogenesis is complex and involves numerous different pathways related to the local hyperglycemic environment, including accumulation of advanced glycosylation end products, oxidative stress injury, and chronic inflammation. Presently, DW is considered a persistent chronic low-grade inflammation. Reportedly, cellular aging and immune damage play a crucial role in DW healing. In wound healing, aging fibroblasts and endothelial cells induce myofibroblast differentiation by secreting platelet-derived growth factor AA, thereby accelerating wound healing. However, high blood glucose interferes with this process, leading to immune cell infiltration and low-grade inflammation of the wound, thus, resulting in delayed wound healing. The cGAS-STING signaling is involved in innate immunity and cytoplasmic DNA can induce STING-dependent inflammatory responses, which play an important role in DW[80]. Geng *et al*[81] reported an increase in STING levels and M1 macrophages in DW tissue from patients and mice. The high reactive oxygen species content released in an HG environment induced mtDNA leakage to the cytoplasm, activated STING signaling, released pro-inflammatory cytokines, induced macrophage polarization to a pro-inflammatory phenotype, and exacerbated endothelial cell dysfunction. Feng *et al*[82] showed that in diabetic mice, STING activation promoted inflammatory response and delayed skin wound healing. STING knockdown and STING inhibitors in the STZ-induced DM mouse model and db/db mouse model inhibited inflammation and promoted wound healing. Yuan *et al*[83] reported that PA-induced inhibition of endothelial angiogenesis was mediated through the dysregulation of the Hippo-Yes-associated protein (YAP) pathway, an important signaling pathway regulating tissue repair and regeneration. PA inhibited endothelial cell proliferation, migration, and tube formation, which was associated with increased macrophage stimulating 1 (MST1) expression, YAP phosphorylation/inactivation, and nuclear repulsion. YAP overexpression or MST1 knockdown could prevent PA-induced inhibition of angiogenesis. PA treatment in vascular endothelium induced mtDNA leakage into the cytoplasm, activating the cytoplasmic DNA sensor cGAS-STING-IRF3 signaling to regulate the Hippo-YAP pathway, thereby inducing MST1 expression, YAP inactivation, and neovascularization inhibition. Audu *et al*[84] investigated the mechanism of macrophages in DW repair and found that increased Jumonji domain-containing protein D3 (JMJD3) in DW macrophages increased the expression of inflammatory genes. RNA sequencing of DW macrophages isolated from the bone marrow cells of JMJD3-deficient (JMJD3 f/fLyz2 Cre+) mice revealed that JMJD3 regulated the STING gene (Tmem173). These findings show the association of STING with chronic inflammation and its role in limiting wound repair and increasing the inflammatory response in diabetic mice. Furthermore, they suggest that cGAS STING plays an important role in the healing of DW.

Table 2 Mechanistic and physiologic effects of cyclic guanosine monophosphate-adenosine monophosphate synthase inhibitors associated with diabetes and its complications

Inhibitor	Mechanism	Physiologic effects
Compound 18	Small molecule inhibitors break the molecular structure of cGAS by binding to hydrogen bonds[91]	Compound 18 improves glucose tolerance in high fat diet mice[94]
RU.521, RU.356, RU332	Competes with ATP and GTP for enzyme binding sites by virtue of its own structural advantages[95]	RU521 attenuates cGAS-STING-mediated cardiac dysfunction in BRG1 knockout diabetic cardiac mice[96]
PF-06928215	Competes with cGMP for the cGAS binding site[97]	PF-06928215 attenuates cGAS-STING-mediated cardiac dysfunction in double knockout of Akt2 and AMPK mice [98]
HCQ	Prevents cGAS from binding to DNA by occupying the DNA binding site[97]	Improvement of inflammation by decreasing IFN-β release from Th1 cells
Aspirin	Aspirin acetylates cGAS to block cGAS-STING signaling. Aspirin's metabolite salicylate may affect NF-κB nuclear translocation[89]	No relevant evidence. Aspirin is only a theoretical cGAS inhibitor because it is easily hydrolyzed in the body
Suramin	Similar to nucleic acid structure, competes for DNA and cGAS binding sites[99]	Suramin blocks dsDNA binding to cGAS and limit AIM2 inflammatory vesicle formation[100]

cGAS: Cyclic guanosine monophosphate-adenosine monophosphate synthase; STING: Stimulator of interferon gene; ATP: Adenosine triphosphate; GTP: Guanosine triphosphate; cGMP: Cyclic guanosine monophosphate; NF-κB: Nuclear factor-κB; Akt: Activated protein kinase B; AMPK: Adenosine monophosphate-activated protein kinase; IFN: Interferon; Th1: T helper type 1; dsDNA: Double-stranded DNA; AIM2: Absent in melanoma 2.

INHIBITORS OF THE CGAS-STING PATHWAY FOR DM AND RELATED COMPLICATIONS

Considerable evidence indicates the contribution of the cGAS-STING signaling pathway to the development of adverse inflammatory and autoimmune responses, which in turn, may exacerbate metabolic disorders. Therefore, the development of cGAS-STING pathway inhibitors is necessary. cGAS and STING inhibitors that have been developed for metabolic diseases are listed in Tables 2 and 3, respectively. However, their clinical application remains elusive, with some of the small molecule inhibitors still in the theoretical modeling stage without known effective doses and pharmacotoxicology, warranting studies to validate these compounds in clinical trials. For instance, the cGAS-STING pathway plays an important regulatory role in tumor development and suppresses tumorigenesis by promoting the cytotoxic effects of T cells and natural killer cells, inducing apoptosis and autophagy. Therefore, the STING signaling pathway exhibits a dual effect on the human body based on its up- or down-regulation[85]. Hence, designed drugs should balance the effects of the STING pathway, rather than completely blocking or activating the pathway. The cGAS-STING pathway can interact with NF-κB, Jun N-terminal kinase, pyroptosis, AMPK, toll-like receptor 4, and mTOR signaling pathways to regulate cellular inflammation and metabolism[86], making the precise designing of targeted drugs to specifically block the STING pathway challenging.

Drug discovery to clinical translation is a time-consuming and expensive process, with an estimated period of 10-15 years, and costs upwards of 1 billion USD before a drug is approved by regulatory agencies and commercialized. Presently, there are two different approaches to drug development, namely phenotype-based drug discovery (PBDD) and target-based drug discovery[87]. PBDD is often used empirically to validate the efficacy of pre-existing compounds against target diseases. For example, suramin, an important drug for treating river blindness and African sleeping sickness, was found to also act as a cGAS inhibitor that blocks the cGAS-to-DNA binding[88]. Elkon[89] reported that aspirin can inactivate cGAS by acetylating the Lys414, Lys384, and Lys39 sites. In PBDD, animal models play an important role because the effects of drugs are sequentially assessed first in cells, followed by tissues or animal models without knowing the specific molecular target. Animal models play an important role in disease pathophysiology, drug target identification, toxicity, pharmacokinetic, and efficacy assessments of novel therapeutic agents, providing substantial basis for transferring the drug from early preclinical studies to later human clinical trials. However, its drawback is that the success rate of drugs subjected to preclinical animal testing remains low in clinical studies. This may be because of the large gap between the preclinical data generated in various standardized animal models of the target disease and the clinical translation gap[90]. Although animal experimental data can help prevent further development of drugs with severe toxicity, they cannot predict subjective drug effects or specific activity, highlighting the importance of selecting a predictable and effective animal model for the overall success of drug discovery and development. The target-based drug discovery approach develops novel targeted drugs based on existing mechanisms. Various novel small molecule compounds have been developed using new molecular technologies utilizing chemical biology, proteomics, and network biology. For example, RU.521 and G150 are recently developed compounds based on the results of high-throughput screening, and the most potent cGA inhibitors. The inhibitor compounds S3, S2, and 18 were developed based on PF-06928215 by using database virtual screening techniques[91]. Additionally, the use of rodents humanized mouse models for preclinical drug safety and efficacy testing of new drugs is considered acceptable and may be more appropriate than that of standard rodents[92]. The establishment of transgenic immunodeficient mice has led to significant advances in these techniques over the past two decades. Transgenic animals have exogenous genes introduced into their genomes. They are typically produced by microinjecting DNA into the prokaryotic nucleus of a fertilized egg, which is subse-

Table 3 Mechanistic and physiologic effects of stimulator of interferon gene inhibitors associated with diabetes and its complications

Inhibitor	Mechanism	Physiologic effects
Nitro fatty acids	Inhibits palmitoylation by binding to STING[101]	Nitro fatty acids protect against mitochondrial damage in hepatocytes of mice with nonalcoholic fatty liver disease[102]
C-176	Covalent small molecule inhibitors. Inhibits STING palmitoylation [103]	C-176 attenuates cGAS-STING pathway-mediated diabetic cardiomyopathy[54]
UNC93B1	The mechanism of action involves the targeting of STING degradation *via* the autophagy-lysosome pathway[104]	Unc93b1 ameliorates neuronal apoptosis induced by high glucose through the TLR9 signaling pathway[105]
SP23	Hydrolysis STING by the ubiquitin-proteasome pathway[106]	Improvement of inflammation by decreasing IFN-β release from Th1 cells

cGAS: Cyclic guanosine monophosphate-adenosine monophosphate synthase; STING: Stimulator of interferon gene; IFN: Interferon; Th1: T helper type 1; TLR9: Toll-like receptor 9.

quently implanted in the fallopian tube of a surrogate mother. Transgenic animals have become a key tool in functional genomics for modeling human diseases and validating new drugs[93]. Overall, the role of experimental animals in the development of novel drugs is crucial, and the development of novel cGAS-STING-targeted drugs may promote the personalized and precision treatment of DM.

CONCLUSION

This review discusses the close relationship between the cGAS-STING pathway and DM and associated complications. The findings showed that inflammation and mitochondrial dysfunction can promote disease progression, and they may be associated with the cGAS-STING pathway. Overall, inhibiting the cGAS-STING pathway can improve disease status and delay the progression of diseases such as IR, NAFLD, DCM, and DNe. This study on the cGAS-STING pathway may provide new insights into the treatment of DM and its complications. This review shows the involvement of the cGAS-STING pathway in different organs, providing a theoretical basis for long-term holistic treatment of multiple organs affected by DM. Future studies may focus on inhibiting cGAS-STING pathway-induced inflammation as a potential therapeutic approach for treating DM and related complications.

FOOTNOTES

Author contributions: Fan MW and Tian JL contributed equally to this study as they are co-first authors of this manuscript. Fan MW, Zhang SH, and Chen Y discussed the data; Tian JL, Chen T, Zhang C, Liu XR, and Zhao ZJ drafted the manuscript and also took responsibility of the data analysis. Zhang SH and Chen Y contributed equally to this study as they are co- corresponding authors of this manuscript.

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