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Review Article

Update on the STING Signaling Pathway in Developing Nonalcoholic Fatty Liver Disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a prevalent chronic liver condition with limited treatment options. Inflammation caused by metabolic disturbances plays a significant role in NAFLD development. Stimulator of interferon gene (STING), a critical regulator of innate immunity, induces the production of interferons and other pro-inflammatory factors by recognizing cytoplasmic DNA to defend against pathogen infection. The STING-mediated signaling pathway appears to play a vital role in hepatic inflammation, metabolic disorders, and even carcinogenesis. Promisingly, pharmacological interventions targeting STING have shown improvements in the pathological state of NAFLD. Macrophages, dendritic cells, natural killer cells, and T cell pathways regulated by STING present potential novel druggable targets for NAFLD treatment. Further research and development in this area may offer new therapeutic options for managing NAFLD effectively.

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Keywords: Stimulator of interferon gene; Macrophage; Innate immunity; Nonalcoholic fatty liver disease.

Abbreviations: AKT, protein kinase B; ATM, ataxia telangiectasia mutated; ATR, ATM and Rad3-related protein kinase; BAX, B-cell lymphoma-2-related protein X; Bcl2, B-cell lymphoma-2; cAIMP, cyclic-adenine monophosphate-inosine monophosphate; c-di-AMP, cyclic dimeric adenosine monophosphate; c-di-GMP, cyclic dimeric guanosine monophosphate; cGAMP, cyclic-guanosine monophosphate-adenosine monophosphate; cGAS, cGAMP synthase; Casp, caspase; CCL, chemokine ligand; CHK1, cell cycle checkpoint kinase 1; CMA, 10-carboxymethyl-9-acridone; di-ABZI, di-amidobenzimidazole; DMXAA, 5,6-dimethylxanthone-4-acetic acid; ER, endoplasmic reticulum; FAA, flavone acetic acid; FFA, free fatty acid; HCC, hepatocellular carcinoma; HSC, hepatic stellate cell; IFI16, interferon inducible protein 16; IFN-1, interferon-1; IKKε, inhibitor of NF-κB kinase epsilon; IL-6, interleukin-6; IR, insulin resistance; IRF3, interferon regulatory factor 3; mtDNA, mitochondrial DNA; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor-kappa B; NK, natural killer; PARP-1, poly (ADP-ribose) polymerase 1; PDL, programmed cell death ligand; SCAP, sterol regulatory element binding protein cleavage-activated protein; STING, stimulator of interferon gene; TBK1, TANK binding kinase 1; TNF-α, tumor necrosis factor-alpha; TRAF6, tumor necrosis factor receptor-associated factor 6.

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Introduction

Owing to the rising prevalence of obesity and type 2 diabetes, nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease, with a global prevalence of around 25%.[1] NAFLD encompasses a spectrum of conditions, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) and even leading to cirrhosis and hepatocellular carcinoma (HCC). The pathogenesis of NAFLD is complex, but inflammation has a crucial role in disease progression.[2] Multiple immune cells and inflammation-related signaling pathways have been implicated in the development of NAFLD.[3] Among these pathways, the stimulator of interferon gene (STING) signaling pathway, an essential regulatory protein in the innate immune system, is capable of sensing double-stranded DNA released by hepatocyte injury or the enterohepatic circulation. This activation of STING leads to liver inflammation, metabolic disturbances, and even carcinogenesis in NAFLD. Moreover, studies have shown that interventions targeting STING can effectively alleviate the pathological state of NAFLD, offering promise for potential novel targeted therapies to improve the prognosis of patients with NAFLD.[4,5]

Innate immunity in NAFLD

The innate immune system has a crucial role in NAFLD pathogenesis, with crosstalk between innate immune cells and liver cells contributing to the disease's initiation and progression. Various genetic and environmental factors lead to excessive lipid accumulation in the liver, triggering pathological reactions like oxidative stress in mitochondria, endoplasmic reticulum (ER) stress and hepatocyte autophagy.[6] Injured or apoptotic hepatocytes release damage-related molecules, such as nucleic acids or proteins, activating liver pattern recognition receptors and alerting the hepatic-innate immune microenvironment in NAFLD. This response involves resident Kupffer cell activation and recruitment of immune cells like neutrophils, monocytes, natural killer (NK) cells and NKT cells, releasing cytokines and chemokines that contribute to inflammation.[7,8] Gut microbiota also plays a significant role in liver inflammation in NAFLD.[9] The gut barrier is a physical barrier that directly prevents the translocation of luminal bacteria and bacterial-derived products or toxins. Because of changes of the intestinal flora in NAFLD, patients can develop compromised intestinal barrier integrity. Consequently, intestinal endothelial permeability, intestinal endotoxins and

Table 1. Similarities and differences of the STING canonical and noncanonical signaling pathways

STING signaling pathway	Canonical model activation	Noncanonical model activation
Depend on STING; Both activate IRF3 and NF-κB		
Activator type	DNA transfection	Etoposide-induced nuclear DNA damage
STING complex composition	cGAS, cGAMP	ATM, PARP-1, TRAF6, P53, IFI16
Transcription factor activation pattern	Predominantly activate IRF3 and moderately activate NF-κB	Predominantly activate NF-κB and moderately activate IRF3
Gene expression profile	Higher levels of the chemokine CXCL10 mRNA and the IRF3-responsive gene ISG56	Higher levels of IL-6 and CCL20 mRNA

ATM, ataxia telangiectasia mutated; cGAMP, cyclic-guanosine monophosphate-adenosine monophosphate; cGAS, cGAMP synthase; CCL20, chemokine ligands 20; CXCL10, CXC-motif ligand 10; IFI16, γ-interferon inducible protein 16; IL-6, interleukin-6; IRF3, interferon regulatory factor 3; ISG56, IFN-stimulated gene 56; NF-κB, nuclear factor-kappa B; PARP-1, poly (ADP-ribose) polymerase 1; STING, stimulator of interferon gene; TRAF6, tumor necrosis factor receptor-associated factor 6.

bacterial breakdown products known as pathogen-related molecular patterns, including nucleic acids, proteins, and flagellin, can cross the gut barrier and be transported through the portal vein to the liver. Then pattern recognition receptors recognize pathogen-related molecular patterns and activate innate immune cells, triggering intracellular signaling cascades and exacerbating inflammatory damage.[10] Notably, DNA released by hepatocytes is considered a crucial factor in inducing sterile inflammation in NAFLD, while microbial DNA derived from the gut also contributes to liver inflammation in this condition.[11,12] The newly discovered STING signaling pathway can identify almost all types of double-stranded DNA and is considered the main pathway for cytoplasmic DNA to induce the NAFLD inflammatory response.[13,14]

STING signaling pathway

STING, also known as the 173 transmembrane proteins, is a critical component of the host's innate immune defense and can contribute to chronic autoimmune, autoinflammatory, and metabolic diseases.[15] STING is primarily localized in ER and is expressed in various immune cells, including macrophages, dendritic cells, NK cells, and T cells. In addition to immune cells, STING is also expressed in endothelial and epithelial cells. These cells are exposed to the external environment and can be susceptible to infectious agents, making STING's presence in these cells significant for detecting and responding to potential threats. Moreover, STING has been implicated in various chronic conditions, including autoimmune, autoinflammatory, and metabolic diseases, highlighting its role in regulating inflammation and immune responses throughout the body.[16,17]

Canonical model of STING activation

STING can be activated by cyclic dinucleotides, such as cyclic dimeric guanosine monophosphate (c-di-GMP), cyclic dimeric adenosine monophosphate (c-di-AMP) and cyclic-GMP-AMP (cGAMP), secreted by intracellular bacteria, or by noncanonical 2′3′-cGAMP generated by cGAMP synthase (cGAS).[18] Involving cGAS and cGAMP in STING-mediation is considered a canonical activation pathway. When abnormal double-stranded DNA (such as pathogen DNA, host cell nucleus, or mitochondrial DNA) is phagocytosed by macrophages, cGAS, the cytoplasmic DNA sensor of pattern recognition receptors, catalyzes ATP and GTP to synthesize the endogenous second messenger cGAMP, which then activates STING in ER.[19] STING then recruits and activates TANK binding kinase 1 (TBK1), which phosphorylates STING and the transcription factor interferon regulatory factor 3 (IRF3) to induce interferon-1 (IFN-1) and other cytokines to exert antiviral and antitumor effects.[20] Furthermore, STING can activate the nuclear factor-kappa B (NF-κB) pathway through a redundant TBK1/inhibitor of NF-κB kinase epsilon (IKKε) mechanism to induce the expression of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[21,22] STING and TBK1 activate the signal transducer and activator of transcription 6, which is consequently phosphorylated. Subsequently, phosphorylated signal transducer and activator of transcription 6 dimerizes and is delivered to the nucleus to induce the expression of chemokine ligand (CCL) 2, CCL20, and CCL26, mediating inflammatory responses.[23] Moreover, the cGAS-STING signaling pathway can induce apoptosis, autophagy, and necrosis.[24–27]

Noncanonical model of STING activation

The STING signaling pathway can be activated independently by cGAS and cGAMP. Additionally, etoposide-induced DNA damage acts as a danger signal in the innate immune system, activating STING through the collaboration of DNA-mediated binding protein γ-interferon inducible protein 16 (IFI16), DNA damage response factors ataxia telangiectasia mutated (ATM), and poly (ADP-ribose) polymerase 1 (PARP-1). This leads to the assembly of an alternative STING signaling complex involving p53 and tumor necrosis factor receptor-associated factor 6 (TRAF6). TRAF6 catalyzes the assembly of K63-linked ubiquitin chains on STING, resulting in the activation of NF-κB, but not IRF3, leading to the expression of an alternative atypical STING-dependent gene program.[28] Table 1 provides a comparison between the canonical and noncanonical signaling pathways of STING, illustrating the similarities and differences between these two pathways.

In summary, the STING signaling pathway plays a pivotal role in the immune system, contributing to antiviral and antitumor immune responses. It is also involved in various inflammatory diseases, including inflammatory bowel disease, NAFLD, unstable angina, and acute myocardial infarction.[29]

STING signaling pathway in NAFLD

Some studies indicate that the expression of STING increases with the progression of steatosis to NASH inflammation and fibrosis, particularly in the hepatic portal vein of patients with fibrosis.[4] In addition, we performed single-cell nuclear sequencing analysis on liver tissues from three healthy individuals and nine NASH patients using the Gene Expression Omnibus dataset GSE212837. The results indicate that the expression of STING in the immune cells and hepatic stellate cells (HSCs) of NASH patients is significantly higher than

	Hepatocyte	Cholangngicyte	Immune	Endothelial	HSCs
CTRL	0	0	817	0	261
NASH	0	0	3777	0	2095

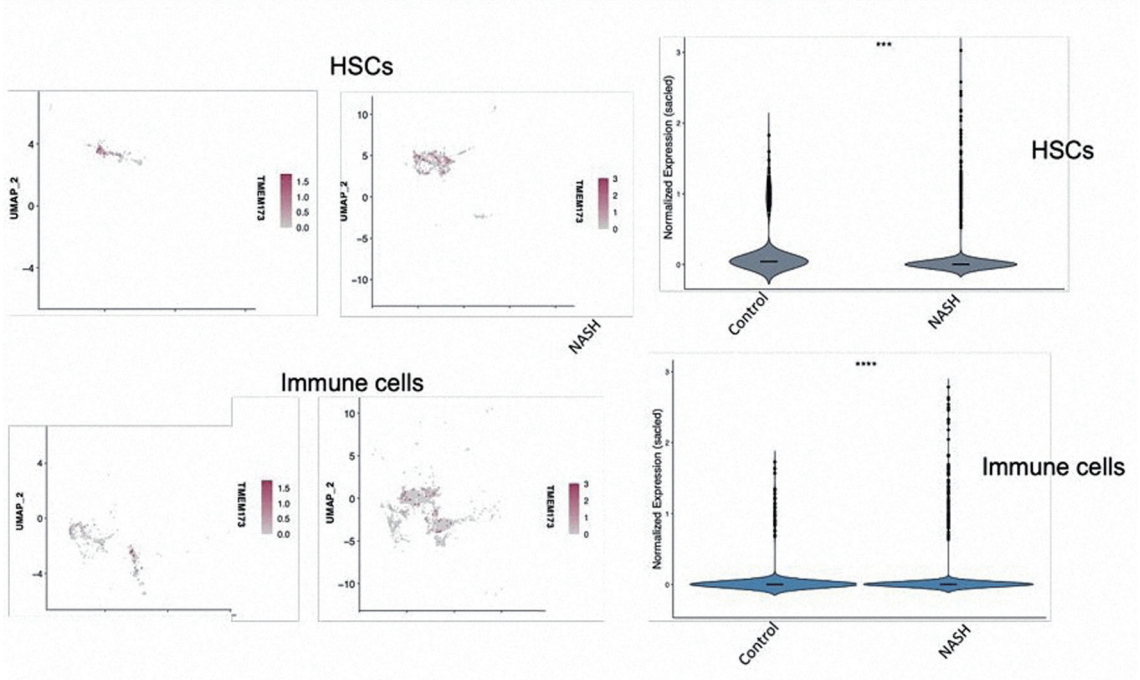

Fig. 1. Expression of STING in liver cells. CTRL, control group; HSC, hepatic stellate cell; NASH, nonalcoholic steatohepatitis; STING, stimulator of interferon gene.

that of the healthy control group (Fig. 1). This suggests that increased STING expression acts as an indicator of NAFLD progression and the severity of liver disease. However, another controversial study reported decreased expression of STING in the liver of NASH patients compared with those with steatosis alone. One possible explanation for this discrepancy could be the absence of fibrosis in the cohort participating in that specific study. Fibrosis is a critical characteristic of advanced NAFLD, and its presence may influence STING expression differently compared to earlier stages of the disease.[30] Studies have also found that the levels of cGAS and STING proteins increased in liver carcinoma patients with the increase in liver fibrosis, and were higher than in the surrounding cancer tissues.[31] These contrasting findings highlight the complexity of the STING signaling pathway's involvement in NAFLD and the need for further research to fully understand its role in different stages of the disease.

Role of STING in NAFL and NASH

The cGAS-STING pathway can activate liver macrophages to induce inflammation and lipid metabolic disorders, IR, and hepatocyte apoptosis. Accordingly, the cGAS-STING pathway likely plays a pivotal role in the progression of NAFLD and NASH (Fig. 2).

Inflammation

The cGAS-STING signaling pathway in the liver can be activated by various factors, including mitochondrial DNA (mtDNA), gut microbial DNA and iron deposition (Table 2). In NASH mice, the content of mtDNA in cytoplasmic mitochondria is significantly higher compared to normal mice, leading to the activation of the STING pathway in hepatic macrophages. This activation induces the expression of NF-κB and pro-inflammatory cytokines like TNF-α and IL-6, contributing to liver inflammation.[32] The mechanism of accumulation of mtDNA in steatotic hepatocytes is likely to interfere with DNA replication by slowing down replication forks and activating the ATM and Rad3-related protein kinase (ATR)/cell cycle checkpoint kinase 1 (CHK1) pathway.[33] Gut microbial DNA-containing extracellular vesicles can be removed by $CRIg^+$ macrophages through complement component C3-mediated opsonization. However, obesity leads to decreased $CRIg^+$ macrophages, and micro extracellular vesicles leakage diffuses into the liver, subsequently activating the cGAS-STING pathway and triggering liver inflammation.[12] Elevated iron concentration in the livers of individuals with NAFLD can also activate the cGAS-STING pathway and cause liver inflammation.[34] STING was unevenly distributed in the liver, mainly expressed in macrophages ($CCR2^+$, $S100A9^+$, Kupffer, and $CD163^+$ cells). In contrast, hepatic sinusoidal endothelial cells ($CD36^+$ cells, HSCs, and SMA^+ cells), and other immune cells were poorly expressed.[4,35] The findings indicate that STING is not expressed in human and mouse hepatic parenchymal cells.[36,37] Subsequent experiments found that transplantation of bone marrow cells from wild-type mice into $STING^{gt}$ mice could exacerbate the severity of liver inflammation and steatosis in $STING^{gt}$ mice, suggesting that macrophage-derived STING is a crucial factor in promoting NAFLD.[38] Under activation of the STING pathway, macrophages can be differentiated into pro-inflammatory M1 macrophages, which can act on liver cells to induce inflammation and fat deposition by secret-

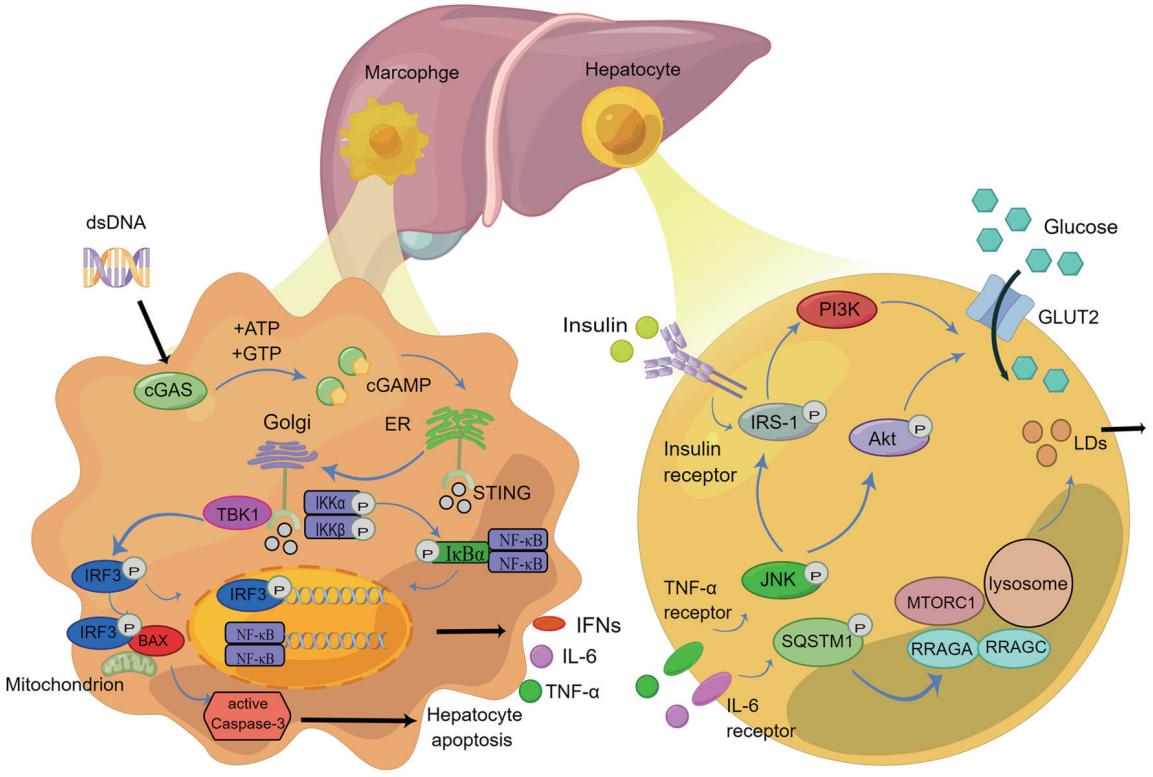

Fig. 2. Activation of the STING signaling pathway in hepatic macrophages. AKT, protein kinase B; BAX, B-cell lymphoma-2-related protein X; cGAMP, cyclic-guanosine monophosphate-adenosine monophosphate; cGAS, cGAMP synthase; dsDNA, double-strand DNA; ER, endoplasmic reticulum; GLUT2, glucose transporter 2; IFNs, interferons; IκBα, inhibitor nuclear factor kappa B alpha; IL-6, interleukin-6; IKK, IκB-kinase; IRF3, interferon regulatory factor 3; IRS-1, insulin receptor substrate 1; JNK, c-jun N-terminal kinase; LDs, lipid droplets; MTORC1, rapamycin target protein complex 1; NF-κB, nuclear factor-kappa B; PI3K, phosphoinositide 3 kinase; RRAGA, ras-related GTP binding A; RRAGC, ras-related GTP binding C; SQSTM1, sequestosome1; STING, stimulator of interferon gene; TBK1, TANK binding kinase 1; TNF-α, tumor necrosis factor-alpha.

ing the inflammatory factors TNF-α, IL-1β and IL-6, consequently promoting NAFLD.[39] However, a few studies suggest that STING exists in mouse hepatic parenchymal cells and activation of the STING/IRF3 pathway induces pro-apoptotic effects in hepatocytes independent of inflammation.[40–42] Hepatic sinusoidal endothelial cells are the most abundant nonparenchymal cells in the liver. When the STING-IRF3 signaling pathway expressed in endothelial cells is activated, the activated IRF3 directly binds to the intercellular adhesion molecule-1 promoter, inducing intercellular adhesion molecule-1 expression in mouse vascular endothelial cells and monocyte-endothelial cell adhesion, promoting the generation of endothelial inflammation.[17] Moreover, liver sinusoidal endothelial cell injury may act as a doorkeeper, implying the progression from NAFLD to the early stage of NASH.[43] The cGAS-STING signaling pathway can also induce TBK1-mediated phosphorylation of p62/sequestosome1 and the formation of hepatic protein inclusions, which are vital indicators for differentiating NAFLD from NASH.[44]

Disordered lipid metabolism

The STING signaling pathway has intricate connections with lipid metabolism, and these interactions play a crucial role

Table 2. Pathological stimuli in NAFLD that activate the STING pathway

Pathological stimuli	Production of pathological stimuli	Mechanisms of promote NAFLD
Mitochondrial DNA	Lipid overload induces nucleotide pool imbalance highlighted by a disruption of replication forks speed and activation of ATR/CHK1 pathway	Induce STING-NF-κB pathway activation and TNF-α and IL-6 expression under lipid overload in the Kupffer cells of liver
Microbial DNA	Deficiency of CRIg$^+$ macrophages and leakage of intestinal EVs containing microbial DNA	Elevate the levels of cGAS expression and STING phosphorylation in hepatocytes and insulin target cells
Iron deposition	High lipid induction enhances the iron accumulation by the upregulation of TFR1 and the down-regulation of FTH1	Upgrade IFN-β and IL-6 expression via the cGAS-STING pathway and induce M1 polarization of macrophage

ATR, ataxia telangiectasia mutated and Rad3-related protein kinase; cGAS, cyclic-guanosine monophosphate-adenosine monophosphate synthase; CHK1, cell cycle checkpoint kinase 1; EV, extracellular vesicle; FTH1, ferritin heavy chain 1; IFN, interferon; IL-6, interleukin-6; NF-κB, nuclear factor-kappa B; STING, stimulator of interferon gene; TFR1, transferrin receptor 1; TNF-α, tumor necrosis factor-alpha.

in the pathogenesis of metabolic disorders like NAFLD. Sterol regulatory element binding protein cleavage-activated protein (SCAP) serves as a cholesterol sensor. A high-fat and high-cholesterol diet can lead to an abnormal increase in macrophage SCAP levels. This, in turn, recruits STING and TBK1 to the Golgi apparatus, activating NF-κB in macrophages. The activation of NF-κB promotes the release of inflammatory factors, enhancing lipid uptake and synthesis in the liver. This highlights the vital role of SCAP as a bridge molecule connecting lipid metabolism and inflammation, contributing to the development of NAFLD.[45] Moreover, the release of mitochondrial DNA in hepatocytes can activate the STING-TBK1 pathway. TBK1-induced sequestosome1 phosphorylation, through STING activation, promotes activation of the rapamycin target protein complex 1 and inhibits lysosomal degradation of lipid droplets. This process leads to excessive lipid deposition in the liver, further exacerbating NAFLD.[46] Furthermore, high-fat diet-induced activation of the STING-IRF3 pathway increases levels of lipid synthase sterol regulatory element binding protein-1c and lowers levels of the lipolytic enzyme peroxisome proliferator-activated receptor alpha.[41] This imbalance promotes lipid synthesis and reduces lipid breakdown, contributing to lipid accumulation in the liver.[47]

Insulin resistance

Chronic low-grade inflammation of metabolic tissues is a central factor in developing IR. The STING signaling pathway may contribute to liver IR through multiple mechanisms, such as blocking insulin signaling pathways and promoting islet β cell senescence and apoptosis. Activating the STING-IRF3 pathway can induce hepatocyte inflammation and promote liver IR and gluconeogenesis by decreasing the expression of insulin signaling (phospho-protein kinase B (AKT)/total-AKT), phosphorylated glycogen synthase kinase 3β, and glycolytic enzymes (glucokinase, phosphofructokinase, and pyruvate kinase), and increasing the expression of glycogen synthase kinase 3β and hepatic gluconeogenic enzymes (glucose-6-phosphatase, phosphoenolpyruvate carboxykinase, and pyruvate carboxylase).[41] Pro-inflammatory factors, including TNF-α and IL-6, can also suppress insulin-induced phosphorylation of AKT on Ser473, inducing IR.[48] Furthermore, the STING pathway affects islet beta cells. Palmitic acid or hydrogen peroxide can activate the cGAS-STING-TBK1 pathway and upregulate pancreatic beta cell senescence indicators, including P21, $P16^{ink4a}$, P53, and p53-binding protein 1. Intervention with the STING inhibitor C176 alleviates pancreatic beta cell senescence, glucose intolerance, and IR.[49] Treating pancreatic beta cells with palmitic acid can activate the STING-IRF3 pathway, which promotes inflammation in pancreatic beta cells and induces apoptosis of pancreatic beta cells by upregulating the expression of apoptosis proteins: B-cell lymphoma-2 (Bcl2)-related protein X (BAX), caspase-3 (Casp-3), and PARP-1.[50]

Hepatocyte apoptosis

The STING-IRF3 signaling pathway in hepatocytes plays a crucial role in inducing apoptosis, and its activation can be triggered by various factors, including ER stress and free fatty acid (FFA) accumulation. In response to ER stress induced by CCl4 or FFA, the STING-IRF3 signaling pathway can lead to the upregulation of pro-apoptotic molecules, such as BAX, as well as apoptotic promoters like Casp-8 and Casp-3. This can subsequently result in hepatocyte apoptosis that contributes to liver injury and disease progression.[40] Studies have shown that inhibiting STING and IRF3 using corresponding siRNAs significantly reduced the FFA-induced inflammatory cytokines and apoptotic signals, including BAX/Bcl2, clv-Casp-3/Casp-3 and clv-PARP/PARP. This suggests that inhibiting STING and blocking the interaction between phospho-IRF3 and BAX and Casp-3 can ameliorate hepatocyte apoptosis and may offer potential therapeutic strategies to mitigate liver injury and hepatocyte death.[41]

Role of STING in NAFLD-liver fibrosis

Liver fibrosis, a consequence of inflammation or death of hepatocytes, is a significant pathological process in various liver diseases. The crosstalk between different cellular pathways, including the STING pathway, contributes to the development of liver fibrosis. TAR DNA-binding protein 43 and X-box binding protein 1 have been identified as factors that promote macrophage self-mitochondrial DNA cytosolic leakage. This leads to macrophage STING activation, triggering intrahepatic inflammation and liver fibrosis.[51,52] Additionally, ER stress-induced liver cell death has been linked to liver fibrosis through the STING-IRF3 pathway. This suggests that liver cell death independently contributes to the development of chemically induced liver fibrosis.[40] HSCs are the primary cell type responsible for liver fibrosis. Studies have shown that treatment of HSCs with macrophages activated through the STING pathway results in increased activation of HSCs, leading to liver fibrosis. This suggests that STING activation in macrophages can promote liver fibrosis through a paracrine mechanism that affects HSCs and other cells involved in fibrosis.[38]

Role of STING in NAFLD-HCC

Indeed, NAFLD-HCC is a serious and feared liver-related complication, imposing a significant health burden. The cGAS-STING signaling pathway has been found to be involved in the occurrence and development of HCC. In HCC cells, sustained high levels of DNA damage can activate the cGAS-STING pathway, leading to the release of IFN-I. The presence of IFN-I can stimulate dendritic cells to migrate to tumor-draining lymph nodes and subsequently cross-activate tumor-specific $CD8^+$ T cells. This process helps control both local and distant tumor growth by enhancing the body's immune response against cancerous cells. Furthermore, the cGAS-STING pathway also has a role in recruiting NK cells and cytotoxic T lymphocytes, increasing the sensitivity of the immune system to attack cancer cells. This process contributes to enhancing the immune-mediated response against HCC cells, potentially providing novel avenues for therapeutic intervention.[53] One limitation is that the upregulation of programmed cell death ligand-1 (PDL-1) and PDL-2 induced by IFNβ and IFN-γ, produced as a result of the cGAS-STING pathway activation, leads to cancer cell immune escape.[54,55] Additionally, the activation of the STING pathway can induce indoleamine 2,3 dioxygenase activation, which promotes tumor immune escape and can suppress T cell activity. This further limits the immune system's ability to target and eliminate cancer cells effectively.[56,57] Moreover, STING activation leads to T lymphocyte apoptosis, allowing cancer cells to escape immune surveillance and evade detection by the immune system.[58] These factors may contribute to the incomplete resolution of tumors after treatment with STING agonists. While the cGAS-STING pathway can trigger short-term inflammation to repress active oncogenes and support an antitumor immune response, prolonged or sustained inflammation leads to tissue destruction and contributes to cancer development or progression.[59] Understanding the delicate balance between the beneficial and potentially det-

Table 3. STING inhibitors for treating NASH/NAFLD liver fibrosis

Drug	Dosage and method of administration	Mechanism	Reference
Remdesivir	20 mg/kg/d (i.g.)	Reduce liver inflammation and lipid metabolism disorders by inhibiting the STING-IRF3 signaling pathway	66
Lingguizhugan decoction	22 g/kg/d (i.g.)	Inhibit the STING-TBK1-NF-κB signaling pathway to reduce liver inflammation	67
Naringenin	100 mg/kg/3 times/week (i.g.)	Inhibit the cGAS-STING pathway thereby reducing the secretion of inflammatory factors by HSCs	68
Sorafenib	10 μmol/L (THP-1 cell culture)	Inhibit the dimerization of STING and the recruitment of TBK1 and IRF3	69,70
Bifidobacterium triple live bacteria powder	0.4 g/mouse/d (i.g.)	Inhibit the STING-NF-κB pathway, thereby inhibiting the release of TNF-α, IL-1β, IL-6 and IFN-β	71

cGAS, cyclic-guanosine monophosphate-adenosine monophosphate synthase; HSC, hepatic stellate cell; IFN, interferon; i.g., intragastric; IL, interleukin; IRF3, interferon regulatory factor 3; NF-κB, nuclear factor-kappa B; STING, stimulator of interferon gene; TBK1, TANK binding kinase 1; TNF-α, tumor necrosis factor-alpha.

rimental effects of the cGAS-STING pathway is essential for developing targeted therapies that maximize its antitumor potential while minimizing unwanted side effects.

STING agonists and inhibitors for treating NAFLD

The STING signaling pathway has emerged as a significant target for the treatment of inflammatory and autoimmune diseases, and the development of STING agonists and inhibitors has become an active area of research. STING inhibitors can be categorized into two main types: covalent and noncovalent inhibitors. Covalent inhibitors work by forming a permanent bond with the target protein, while noncovalent inhibitors do not form such a bond and can be reversible in their action. Palmitoylation of the STING protein is necessary for its activation, and C176, C178, H151, and NO_2-cLA covalently bind to STING to inhibit palmitoylation thereby leading to pathway inactivation.[60,61] Noncovalent inhibitors control the activation of STING by competitively reducing the binding of 2′,3′-cGAMP to STING, mainly including astin C, SN-011, compound 18, gelsevirine, and palbociclib.[62–66] Although many STING inhibitors have been discovered, none have been used for the treatment of NAFLD. However, studies have found that some drugs are effective for alleviating the pathological state of NAFLD by inhibiting the STING pathway (Table 3).[66–71] Remdesivir was shown to significantly reduce liver inflammation and lipid metabolism disorders in NAFLD mice by inhibiting the STING-IRF3 signaling pathway.[67] Lingguizhugan decoction and its critical components cinnamaldehyde, atractylenolide II and glycyrrhizinate can significantly reduce liver inflammation levels by inhibiting the STING-TBK1-NF-κB signaling pathway in hepatic Kupffer cells, subsequently decreasing lipid deposition in hepatocytes and effectively relieving NAFLD progression.[68] Naringenin was shown to reduce liver inflammation and HSC activation by inhibiting the cGAS-STING signaling pathway, improving liver fibrosis.[31] Sorafenib may attenuate the signal transduction of the STING pathway by inhibiting the dimerization of STING and the recruitment of TBK1 and IRF3, thereby alleviating liver inflammation and fat accumulation induced by palmitic acid.[69,70] *Bifidobacterium* triple live bacteria powder relieves HFD-induced NAFLD by inhibiting the expression of STING, thereby inhibiting the release of TNF-α, IL-1β, IL-6, IFN-β and p-NF-κB p65 induced by macrophages.[71]

STING agonists are currently under active development. Cyclic dinucleotides directly stimulate STING, including c-di-GMP, c-di-AMP, 3′,3′-cGAMP and 2′,3′-cGAMP.[72] However, because of the instability, negative charge, and hydrophilicity of cyclic dinucleotides that limit their use, nonnucleotide agonists have been developed, such as 5,6-dimethylxanthone-4-acetic acid (DMXAA), flavone acetic acid (FAA), 10-carboxymethyl-9-acridone (CMA), di-amidobenzimidazole (di-ABZI), etc.[73–75] STING agonists were found to improve the efficacy of NAFLD-HCC treatment (Table 4).[5,76-80] The STING agonist 3′3′-cyclic adenine monophosphate-inosine monophosphate (cAIMP) was shown to reduce tumor burden by increasing tumor cell apoptosis early in HCC.[5] STING agonist 2′,3′-cGAMP downregulated macrophage inhibitory receptor signal-regulatory protein alpha and inhibited the CD47/signal-regulatory protein alpha signaling axis, which mediates phagocytosis and escape of liver tumor cells, and enhances the phagocytosis of liver tumor cells by macrophages.[76] To ensure the safety and efficacy of treatment, some studies have combined STING agonists with traditional antitumor therapies such as surgery and immunotherapy to have better therapeutic effectiveness, which has become a research hotspot. Irreversible electroporation, an ablation therapy, leads to tumor cell death through apoptosis. Compared with irreversible electroporation alone, STING agonist c-di-GMP combined with irreversible electroporation increased tumor-infiltrating IFN-γ/TNF-α production by CD4 and CD8 cells. The number of T cells induced a stronger antitumor immune response.[77] As the first STING-based cancer vaccine in immunotherapy, STINGVAX can enhance T lymphocyte infiltration into cancer tissues by upregulating PDL-1.[78] Combining DMXAA, cisplatin, tumor-specific peptides, neoantigens and an immune checkpoint inhibitor can induce the priming of tumor-specific $CD8^+$ T cells to enhance the immune response, resulting in an anticancer immune synergistic effect.[79] Synergistic immunotherapy with silk hydrogel containing interferon genes agonist, Hepa1-6 liver cancer-specific neoantigen and toll-like receptor 9 agonist, and mucin domain 3 antibody significantly reduced regulatory T cells and increased IFN-γ and IL-12p70 levels in tumor tissue, promoted IFN-γ^+CD8^+ T cell and 41BB$^+$CD8$^+$ T cell infiltration, and significantly inhibited HCC progression.[80] Moreover, chemotherapy and radiotherapy combined with the STING pathway can inhibit tumor progression. Using paclitaxel, a commonly used chemotherapeutic drug in HCC, stabilizes microtubules. It interferes with mitosis, cGAS-dependent IRF3 phosphorylation accumulates, and the transcriptional mechanism promotes apoptosis. Combining cGAS-STING pathway activation and

Table 4. STING agonists for treating NAFLD-HCC

Drug	Combination	Dosage and method of administration	Mechanism	Reference
3′3′-cAIMP	/	2 μg/g/3 times/ week (i.p.)	Increase tumor cell apoptosis by activating STING	5
2′,3′-cGAMP	/	1 μg/mL (THP-1 cell culture)	Enhance the phagocytosis of liver tumor cells by macrophages	76
c-di-GMP	Irreversible electroporation	1 mg/mL (intratumoral injection)	Increase tumor-infiltrating IFN-γ/ TNF-α production of CD4 and CD8	77
CDA/CDG	Granulocyte-macrophage colony-stimulating factor	20 μg/mouse (s.c.)	Enhance T lymphocyte infiltration into cancer tissues by upregulating PDL-1	78
DMXAA	Cisplatin, tumor-specific peptides, neoantigens, and an immune checkpoint inhibitor	100 μg/mouse (s.c.)	Induce the priming of tumor-specific $CD8^+$ T cells to enhance the immune response	79
cGAMP	Hepa1-6 liver cancer-specific neoantigen and toll-like receptor 9 agonist, and TIM-3 antibody	30 μg/mouse (i.p.)	Reduce regulatory T cells and increase IFN-γ and IL-12p70 levels in tumor tissue, promote IFN-$γ^+CD8^+$ T cell and 41BB^+CD8^+ T cell infiltration	80

AIMP, adenine monophosphate-inosine monophosphate; CDA, cyclic di-adenosine monophosphate; CDG, cyclic di-guanosine monophosphate; DMXAA, 5,6-dimethylxanthone-4-acetic acid; GAMP, cyclic-guanosine monophosphate-adenosine monophosphate; GMP, guanosine monophosphate; HCC, hepatocellular carcinoma; IFN, interferon; IL, interleukin; i.p., intraperitoneal; PDL-1, programmed cell death-1; s.c., subcutaneous; STING, stimulator of interferon gene; TIM-3, T cell immunoglobulin and mucin domain 3; NAFLD, nonalcoholic fatty liver disease.

paclitaxel significantly inhibited tumor growth.[81] Radiotherapy-induced DNA damage leakage into the cytosol can trigger the host antitumor immune response, using alginate as a carrier to deliver Mn^{2+} into radiotherapy-treated tumors. Synergistically accumulated cytosolic DNA can synergistically amplify the activation of the cGAS-STING pathway, thereby enhancing radiotherapy-induced antitumor immunity.[82]

Conclusion and future perspectives

Abundant evidence has established a close connection between innate immune activation and NAFLD.[83] STING, being a crucial component of the innate immune system, is highly enriched in liver macrophages. Studies have explored how the STING signaling pathway mediates macrophage-mediated hepatic immune responses and metabolic regulation in NAFLD. While STING activation enhances immune surveillance in the liver during pathogen infection and tumors, its continuous activation can lead to a micro-inflammatory state in the liver. This, in turn, induces abnormalities in lipid metabolism, IR, and hepatocyte apoptosis, ultimately accelerating liver fibrosis and HCC development. Inhibiting STING has shown promise in treating inflammatory diseases, offering potential new avenues for NAFLD treatment. However, it is essential to consider potential side effects when activating the pathway, as STING's effects can be double-edged—either suppressing cancer through early inflammation or promoting cancer through persistent chronic inflammation. Therefore, in addition to using STING agonists as monotherapy for tumors, combining STING agonists with traditional antitumor therapies such as surgery, chemotherapy, radiation therapy, and immunotherapy may minimize the negative effects. Although STING agonists or inhibitors have demonstrated encouraging results in treating NAFLD, there are still some deficiencies to be further studied. Firstly, there are currently no clinically relevant diagnostic indicators developed for the STING signaling pathway, and it is worth exploring the biochemical markers of STING in mouse models or *in vitro* samples. Secondly, research on the pathological mechanisms of the STING signaling pathway in NAFLD is still not comprehensive and needs further improvement. Furthermore, current research mainly focuses on basic experimental studies and lacks the application of clinical trials. Further scientific and standardized clinical research is needed to verify their effectiveness and safety, which will assist in the development of clinical treatment guidelines. Such research efforts will be critical in developing effective therapies for NAFLD and related conditions.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Contributed equally to this work (WL, ZZ), and provided intellectual input to the Editorial (All authors).

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