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REVIEW

STING and liver disease

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Abstract STING (stimulator of interferon genes) also known as transmembrane protein 173 (TMEM173) is a cytoplasmic DNA sensor which can be activated by the upstream cyclic dinucleotides (CDNs). This activation produces cytokines such as interferons and pro-inflammatory factors via the downstream IRF3 and NF-κB pathways, triggering an innate immune response and adaptive immunity to maintain homeostasis. STING is mainly expressed and activated in non-parenchymal cells, thus exerting a corresponding effect to maintain the homeostasis of the liver. In viral hepatitis, interferons and pro-inflammatory factors produced after STING activation initiate the immune response to inhibit virus replication and assembly. In the case of metabolic diseases of the liver, the activation of STING in kupffer cells and hepatic stellate cells leads to inflammation, the proliferation of connective tissue, and metabolic disorders in the hepatocytes, promoting the occurrence and development of the disease. In hepatocellular carcinoma, STING has two contradictory roles. When STING is activated in dendritic cells and macrophages, a large number of cytokines can be produced to initiate innate immune effects directly and to exert adaptive immunity through the recruitment and activation of T cells; however, aberrant activation of the STING pathway leads to a weakening of immune function and promotes oncogenesis and metastasis. Here, we summarize the interactions between STING and liver disease that have currently been identified and how to achieve therapeutic goals by modulating the activity of the STING pathway.

Keywords STING · Viral hepatitis · Non-alcoholic fatty liver disease · Liver fibrosis and cirrhosis · Hepatocellular carcinoma

Molecular regulation of STING and its signaling pathways

STING, also known as MITA, MPYS, ERIS, and TMEM173, is an endoplasmic reticulum (ER) associated dimeric protein that was discovered in 2008 [1–4]. STING consists of an N-terminal domain that spans the ER membrane four times, and a cytoplasmic C-terminal region, which contains the ligand-binding domain (LBD) and the C-terminal tail [5]. STING is mainly distributed in various tissues and organs, and its expression in tissue cells can be controlled by gene regulation. Hypermethylation of CpG land in the STING promoter interferes with STING transcription and downregulates STING expression levels [6]. Transcription factors CREB and c-Myc can combine with human STING (hSTING) promoter to enhance its transcription activity to increase the expression level of STING [7]. STING splicing isoform, including MITA-related protein (MRP), negatively downregulates STING-induced interferon (IFN) production [8]. MicroRNAs bind to the 3'-untranslated region of hSTING to silence STING translation process and decrease the expression level of STING at the post-transcriptional level [9]. Post-translational modifications (PTMs) of STING can also modulate STING function. Palmitoylation at the STING Cysteine

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88/91 is critical for the recruitment and activation of TANK-binding kinase 1 (TBK1) and interferon regulatory factor 3 (IRF3) [10]. In addition to activating STING–TBK1 pathway, which elicits the release of IFNs to exert anti-viral effects, polyubiquitination of STING can also degrade STING and abrogate its effects [11]. TBK1 and IκB kinases (IKK) directly phosphorylate STING and then recruit IRF3 to produce IFNs [12].

In the cytoplasm, activation of STING is mainly through recognition and binding of exogenous cyclic dinucleotides (CDNs) such as cyclic diguanosine monophosphate (c-di-GMP) and cyclic diadenylate monophosphate (c-di-AMP) produced by bacteria or endogenous CDNs including cyclic GMP–AMP (cGAMP). When ectopic DNA appears in the cytoplasm, including exogenous DNA produced by viruses and bacteria, and endogenous DNA such as nuclear DNA and mitochondrial DNA, cyclic GMP-AMP synthase (cGAS) as a DNA sensor can detect and bind to cytoplasmic DNA. Subsequently, cGAS is converted to cGAMP, which binds and activates STING [13]. Some RNA viruses trigger the release of cytoplasmic mtDNA to activate cGAS–STING signaling pathway [14]. Upon binding of CDNs, STING undergoes a conformational change and transfers from the ER to the Golgi [15]. Subsequently, STING recruits and activates TBK1 and IRF3, which translocate to the nucleus for transcriptional production of IFNs [1]. STING can also interact with IKK complexes, including IKKα, IKKβ, and IKKε. Among them, IKKε can synergistically phosphorylate IRF3 with TBK1, while IKKβ and IKKα activate NF-κB [12]. Activated NF-κB dimers enter nucleus to transcribe pro-inflammatory factors, including IL-1β, IL-6, and TNF-α [12]. Cytokines such as IFNs and pro-inflammatory factors initiate innate immune responses to eliminate intracellular pathogens, and activate antigen-presenting cells (APCs) to cross-presentation antigens to T cells, thereby triggering an adaptive T-cell immune response [1, 12]. In addition, STING activation can induce non-immunological reactions such as cell autophagy, senescence, apoptosis, and necrosis [16] (Fig. 1).

STING is not homogeneously distributed in liver. Compared to hepatocytes, STING is mainly expressed and activated in hepatic non-parenchymal cells (NPCs), including Kupffer cells, sinusoidal endothelial cells, and hepatic stellate cells (HSCs). Exogenous pathogens mainly infect hepatocytes, so the effects of STING in liver are mainly exerted through cellular cross-talking [17].

This review summarizes the current interaction between STING and liver diseases and how to exogenously regulate STING activity to achieve therapeutic effects.

Viral hepatitis type B

HBV is an enveloped double-stranded DNA virus and HBV genomic DNA is a relaxed circular double-stranded DNA molecule (rcDNA). After HBV invades hepatocytes, HBV genome enters the nucleus, at which point rcDNA is extended and converted into covalently closed circular DNA (ccDNA). HBV uses cccDNA as a template to transcribe four mRNA. The longest 3.5 kb fragment is called pre-genomic RNA (pgRNA), carrying all genetic information. The pgRNA is used as a template to generate offspring rcDNA to form a new HBV [18].

Currently, it has been shown that STING activation can produce IFNs to inhibit HBV replication [19–24]. The polymerase polymorphism rt269I in HBV genotype C and telomerase-derived 16-mer peptide GV1001 cause mitochondrial stress and release mtDNA in human HCC cell line HepG2, which activates STING–TBK1–IRF3 pathway and produces IFN-β to exert anti-viral effects [19, 20]. However, STING mainly activates downstream TBK1–IRF3 pathway, whereas MRP only activates IKK–NF-κB pathway to inhibit HBV replication [22]. Besides, ISG56 produced by cGAS–STING pathway in human hepatoma Li23 cell inhibits viral assembly without influencing HBV DNA expression [25].

Although STING can inhibit HBV replication and assembly, HBV still causes persistent liver infection. In terms of HBV itself, when HBV invades human hepatoma HepG2-hNTCP cells, little immunostimulatory HBV DNA is produced, and HBV genome is packaged by viral capsids to escape cGAS recognition [26, 27]. In addition, several studies have shown that HBV can inhibit STING mRNA expression [27, 28]. The anti-viral effect of K63-linked STING polyubiquitination is diminished after STING binds to the RT and RH sites on HBV DNA polymerase [17, 29].

Currently, to address the low expression of STING in hepatocytes, we can exogenously introduce STING plasmids into hepatocytes or apply STING agonists [17, 30]. The treatment of HBV with anti-viral drugs can be accompanied by the use of methylation inhibitors to inhibit STING promoter methylation, thus improving the therapeutic effect [31]. The latest findings show that manganese (Mn^{2+}) promotes the production of type I interferon and inhibits HBV replication by enhancing the affinity between STING and cGAMP [32].

Viral hepatitis type C

HCV is a single positive-stranded RNA virus and HCV genome is composed of non-coding regions (NCR) at the 5'-terminal and 3'-terminal and an open-reading frame
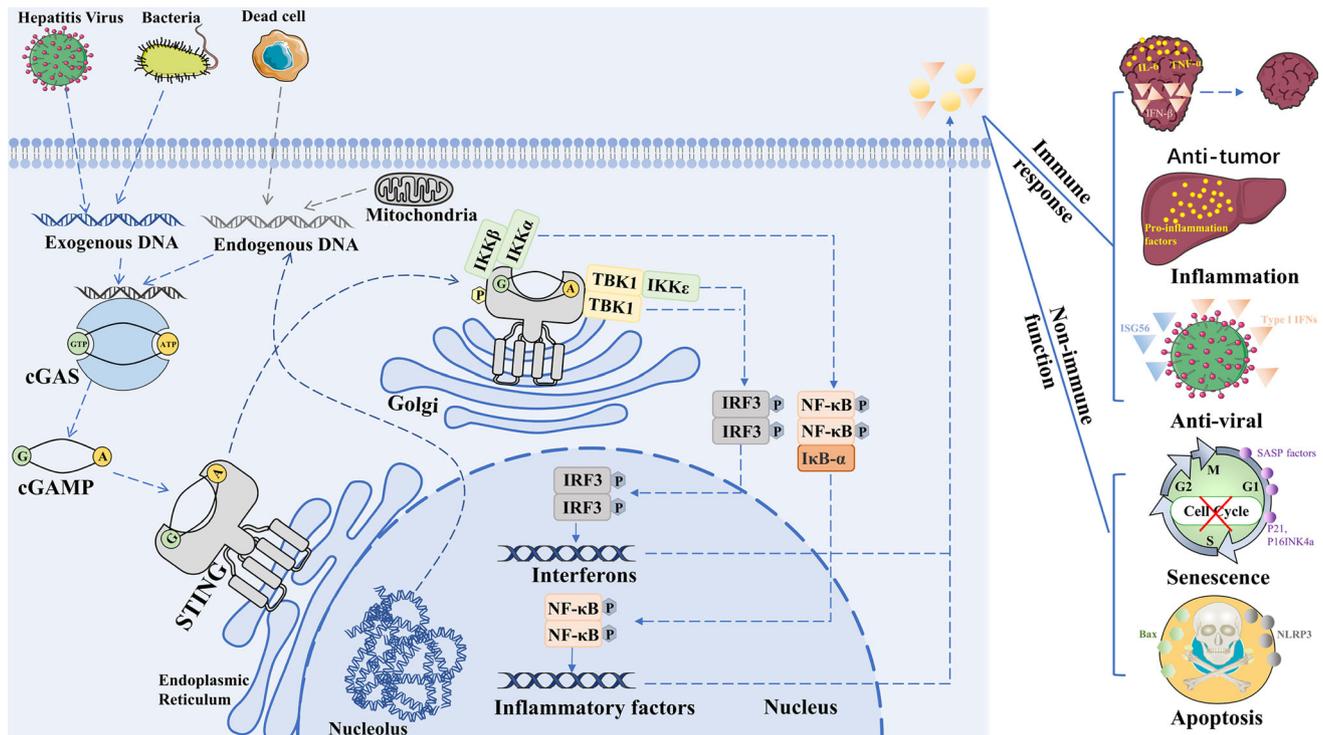
Fig. 1 cGAS–STING signaling pathway in liver immune cells. When exogenous pathogens such as viruses and bacteria invade cells, the released exogenous DNA and endogenous host DNA are recognized by cGAS and activate STING through the production of cGAMP. The activated STING produces a large number of cytokines such as interferons and inflammatory factors mainly through the downstream TBK1–IRF3 and IKK–NF-κB signaling pathways. After these cytokines are released extracellularly, they can exert immunological effects such as anti-cancer, anti-viral, inflammation, and non-immunological effects such as cell senescence and apoptosis

(ORF) in the middle. Starting from the 5'-terminal of the ORF, the coding region consists of seven gene regions, including NS3 and NS4 [33].

Yi et al. found that STING not only generates type I IFNs and ISGs through TBK1–IRF3 pathway to initiate anti-viral responses, but also silences HCV 1b/Con1 replicon replication in human hepatoma Huh7.5 cells [34].

Similarly, HCV can inhibit STING and its pathway. Several studies have shown that the HCV NS4B protein can interact directly with STING because of its N-terminal structure similar to that of STING. This interaction disrupts the interaction of STING with mitochondrial anti-viral signal (MAVS), to attenuate retinoic acid-inducible gene I (RIG-I)-induced IFN-β production in Huh7.5 cells [35]. Since both are located in the ER, the interaction of HCV NS4B and STING limits the positional transition of STING to disrupt the interaction between STING and TBK1 in PH5CH8 cell (an immortalized human hepatocytes cell line) [36]. In the above process, NS3/A can collaborate with NS4B to inhibit STING activity and IFNs production [35, 36]. Further researches reveal that, unlike HCV genotype 1b Con1 replicon, STING has no inhibitory effect on HCV 2A/JFH1 replicon. However, HCV 2A NS4B,

especially in the B region, can inhibit STING aggregation and attenuates STING-mediated anti-viral effects [34].

Currently, it has been found that inoculation of recombinant baculovirus into HCV-infected hepatocytes reactivates STING and initiates STING-mediated immune responses [37].

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is a metabolic stress liver injury associated with insulin resistance and genetic susceptibility, including simple fatty liver, non-alcoholic steatohepatitis (NASH), and its associated cirrhosis and liver cancer [38].

It has been found that NASH patients have an abnormal liver mitochondrial function and significantly higher cytoplasmic mtDNA content than normal [39]. When hepatic phagocytes engulf apoptotic or dead hepatocytes, their self-DNA enters the cytoplasm and then activates cGAS–STING pathway [40]. Besides, excessive deposition of lipids in NAFLD patient liver leads to oxidative stress damage to ER, thus activating STING–TBK1 pathway and promoting hepatic inflammation [41].

Most studies have found that activation of STING–TBK1–IRF3 and IKK–NF-κB pathways in hepatic phagocytes from high-fat diet (HFD) feed wild-type mice (STING$^+$, C57BL/6J background) produces cytokines, including IFNs, inflammatory factors, α smooth muscle actin (aSMA), TGF-β, and type IA collagen A1 (Col1a1). Of these, IFNs and inflammatory factors mainly act on mouse hepatocytes, causing abnormal inflammation in liver [42–45]; whereas aSMA, TGF-β, and Col1a1 mainly activate HSCs and exacerbate liver fibrosis through paracrine secretion [42, 43, 45]. Besides, activation of STING–TBK1 pathway in HFD-feed WT mouse liver not only causes hepatic metabolic disturbances, including insulin resistance and lipid deposition in hepatocytes [42, 44], but also increases P62 phosphorylation levels and deposits insoluble P62 protein inclusions, which play an important pathogenic role in the formation of NASH [46]. However, some scholars have questioned whether these findings obtained from mice are suitable for humans, so further studies and elaborations are warranted [47].

Liver fibrosis and cirrhosis

Hepatitis virus, alcohol, and autoimmune factors can contribute to the development of liver fibrosis, which then progresses to cirrhosis. Certain pathogenic factors, such as viruses and fat deposits, can activate STING and STING–TBK1-mediated inflammatory responses [48]. Through cellular interactions and signal transduction, inflammation further activates HSCs and converts them into myofibroblast-like cells, which secret α-SMA and hepatocyte growth factors to accelerate the formation of hepatic fibrosis [42, 43]. Besides, in CCl4-treated WT mouse hepatocytes, ER stress caused extensive phosphorylation of TBK1 and IRF3 through STING. At this time, mouse hepatocytes apoptosis occurred and the degree of hepatic fibrosis increased. This phenomenon had not been observed in STING-deficient mice [49]. Therefore, STING-mediated liver inflammation and hepatocyte death are the two main direct drivers of liver fibrosis.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common subtype of primary liver cancer with a high mortality rate [50]. Unlike normal cells, the cytoplasm of hepatocellular carcinoma cells contains large amounts of ectopic DNA, such as tumor-derived DNA, mtDNA, and nuclear chromosome fragments [51]. When cytoplasmic DNA is recognized by cGAS in DCs and macrophages, STING–TBK1–IRF3 and IKK–NF-κB pathways are activated to produce IFNs, pro-inflammatory factors, and chemokines to restrict tumor cells proliferation. These cytokines also recruit DCs and NK cells around tumor tissues, forming a tumor-suppressive microenvironment infiltrated by tumor-specific lymphocytes and acting as a front-line defense against tumor immunity [52]. Besides, IFN-β not only enhances the terminal differentiation of DCs and accelerates the maturation of DCs, promoting the cross-presentation of tumor-specific antigenic peptides from DCs to MHC class I molecules in CD8 + T cells to activate it [53], but also increases CXCL9, CXCL10, and other chemokine expression, which in turn induces T-lymphocytes to metastasize to tumor tissues, killing tumor cells and initiating adaptive immune responses [54]. Studies have found that when cGAS–STING pathway is activated in senescent liver fibroblasts or epithelial cells, large amounts of pro-inflammatory factors, chemokines, growth factors, and proteases are secreted via STING–IKK–NF-κB signaling pathway, which is a typical feature of cellular senescence, also known as SASP [55]. SASP can stimulate inflammation in surrounding tumor tissue through paracrine and autocrine forms, accelerating senescence of cancer and precancerous cells, and also recruits NK cells and neutrophils to clear cancerous tissue [56, 57]. Besides, STING activation produces non-immune functions, including autophagy, apoptosis, and necrosis, which effectively remove exogenous pathogens and cancer DNA and also facilitate antigen presentation to T cells to mediate T-cell immune responses [58].

Conversely, STING signaling pathway promotes tumorigenesis and progression. IFN-β generated by STING–TBK1–IRF3 pathway stimulates the production of immune checkpoint molecules, such as programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which bind to T-cell surface receptors to inhibit T-cell activation, resulting in immune evasion [59, 60]. Besides, type I IFNs can induce persistent DNA damage during treatment with chemotherapy and radiotherapy techniques, which in turn aberrantly activate STING and cause long-term inflammation [61]. The latter causes tissue destruction and immunosuppression, decelerating cancer cell senescence and immortalizing cancer cells [57]. SASP secreted by HSCs was found to promote the formation of obesity-associated HCC [62]. Besides, STING-induced apoptosis of T and B lymphocytes impairs cellular immune functions [63].

For the treatment of HCC, Huang et al. found that tumor-targeted lipid-dendritic calcium phosphate nanoparticles (TT-LDCP) activate STING–TBK1–IRF3 pathway and increase the expression of IFNs, pro-inflammatory factors, and chemokines, causing DCs' aggregation into tumor microenvironment to increase CD8 + T-cell infiltration and activation and inhibit HCC progression

[64]. STING agonists can be used in combination with immune checkpoint inhibitors (ICIs). T-lymphocytes can be activated and infiltrate tumor tissue using STING agonists. At this point, ICIs, such as anti-PD-L1 and anti-CTLA-4 antibodies, restore T-cell immune function to consistently suppress tumor growth and metastasis [65, 66]. Besides, STING can be used in combination with chemotherapy and radiotherapy. Ionizing radiation and drug factors damage the genome of tumor cells, which in turn releases tumor dsDNA and activates cGAS–STING pathway in hepatic NPCs [67].

Other liver diseases

Alcoholic liver disease is mainly caused by long-term heavy alcohol consumption. In the early stages of alcoholic liver injury in WT STING$^+$ C57BL/6J mice, alcohol induces hepatic ER stress via cytochrome P450, which then activates STING–TBK1–IRF3 pathway. Phosphorylated IRF3 binds to the intracellular pro-apoptotic molecule B-cell lymphoma 2-associated X protein and transits into mitochondria, initiating intracellular apoptotic signaling that causes apoptosis of hepatocytes. This apoptotic process is not associated with type I IFNs or inflammation. Differently, in the late stage of alcoholic liver disease, STING–TBK1 pathway activation is mainly through the recognition of damaged hepatocyte nuclear DNA by cGAS [68].

Liver dysfunction and radiation-induced liver disease occur during radiation therapy for HCC. Ionizing radiation causes apoptosis and necrosis in WT mouse hepatocytes, and hepatocyte self-DNA escapes and accumulates in the hepatic blood sinusoids. cGAS–STING pathway in hepatic NPCs recognizes and binds ectopic DNA in the blood sinusoids, producing type I IFNs and pro-inflammatory factors. Type I IFNs down-regulate the levels of superoxide dismutases (SODs) and increase the expression of reactive oxygen species (ROS) in hepatocytes, causing intracellular oxidative stress and sustained damage. Besides, type I IFNs induce the expression of CXCL10 and IFIT1 in hepatocytes, further aggravating mouse liver injury [69].

In addition to the above chemical liver injury, hepatic ischemia–reperfusion (IR) injury is also associated with STING. MicroRNA-24-3p was found to bind STING UTR to down-regulate the expression level of STING and inhibit phosphorylation of IRF3. In this process, the release of inflammatory factors was reduced and hepatic IR injury was alleviated, laterally suggesting that STING can promote the occurrence of hepatic ischemia–reperfusion injury in male mice [9]. Similarly, Wang et al. found that hepatic IR injury was also closely related to STING–NLRP3 axis. Following liver post-IR injury, aged mice hepatocytes release mtDNA, which activates cGAS–STING pathway in hepatic macrophages to produce inflammatory factors and chemokines, including nuclear binding domain and leucine-rich repeat protein 3 (NLRP3). Increased activation of NLRP3 further upregulates inflammatory factor expression levels to exacerbate liver IR injury [70].

STING agonists and antagonists

STING agonists include natural CDNs, synthetic CDN agonists, and non-cyclic dinucleotide molecules. As ligands for STING, CDNs and CDN analogs such as 3'3'-cAIMP can directly bind the C-terminus of STING [71, 72]. In addition to the above two categories, there are several non-CDN small-molecule STING agonists, including DMXAA, CMA, DSDP, G10, and BNBC. DMXAA and CMA can bind directly to the mSTING C-terminal domain to activate STING and thus exert anti-viral effects [73, 74]; while G10 promotes phosphorylation of hSTING [75]. Besides, further studies are needed to elucidate how DSDP and BNBC activate STING [76, 77].

In the liver, CDN agonists and synthetic CDN agonists such as 3'3'-cAIMP, cGAMP, and c-di-AMP enhance the cross-talk between hepatocytes and immune cells. IFNs, ISGs, and chemokines produced after the activation of STING signaling pathway in immune cells can induce hepatocyte apoptosis and autophagy, and initiate immune responses to inhibit viral infection and hepatocarcinogenesis [71, 78, 79]. Differently, CMA and DMXAA can directly activate mSTING in hepatic macrophages to increase IFNs and pro-inflammatory expression, ultimately causing hepatic steatosis and inflammation [43, 80, 81] (Fig. 2a; Table 1).

In the application of STING inhibitors, STIM1, as a calcium sensor, was found to attach STING to ER and limit position change after STING activation [82]. C-178 and C-176 can covalently bind to Cys91 on mSTING and reduce the palmitoylation of mSTING, with C-178 mainly inhibiting ISGs expression and C-176 predominantly reducing IFN-I expression. Similarly, H-151 irreversibly binds to Cys91 in hSTING to inhibit hSTING palmitoylation [83]. Currently, these STING agonists are used to inhibit the activation of STING and reduce the expression of IFNs and inflammatory factors to alleviate autoimmune diseases and auto-inflammatory diseases. RDV inhibits the secretion of inflammatory factors and attenuates liver inflammation by significantly eliminating the phosphorylation of STING and its downstream IRF3 and NF-κB pathways [84] (Fig. 2b; Table 1).

Fig. 2 The different effects of using STING agonists and inhibitors in the liver. In the case of STING agonists, they mainly exert anti-viral and anti-cancer effects through the IFN produced, while for antagonists, they are currently mainly used to alleviate liver inflammation
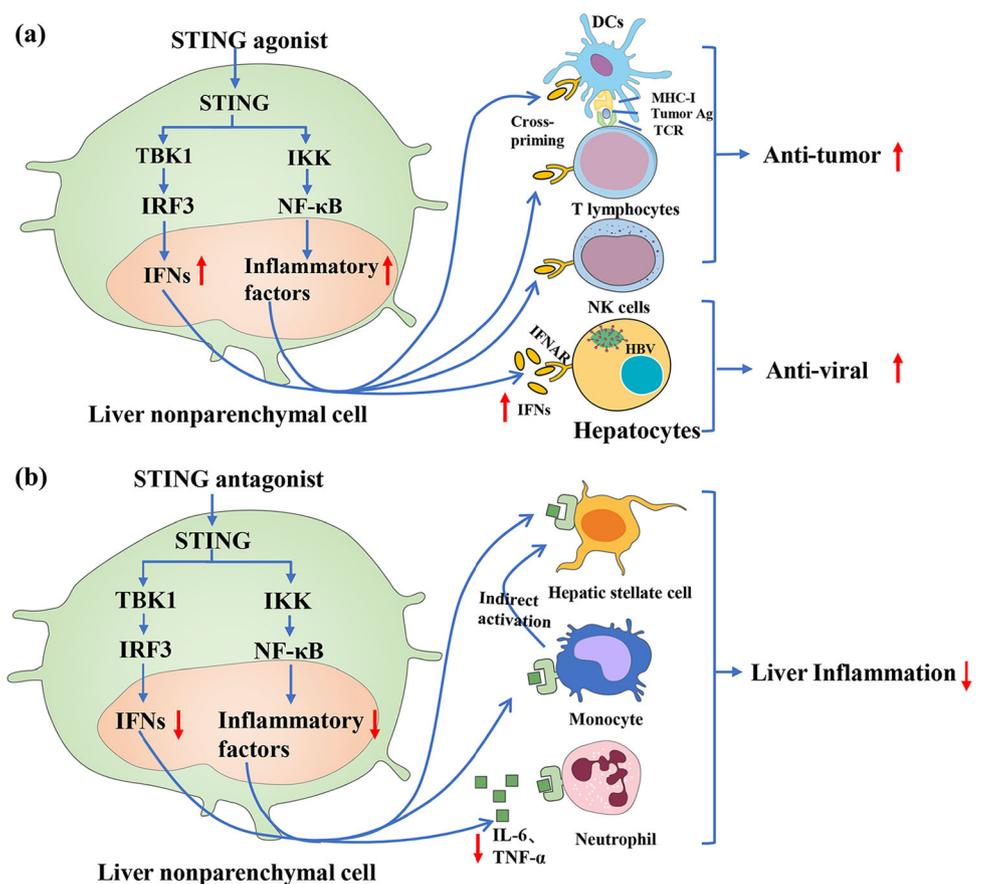

Table 1 Overview of STING agonists and antagonists in liver disease

Type		Related to hSTING	Ways to activate/inhibit STING	Effects on liver disease	References
Agonists	c-di-AMP	Yes	It directly binds the CTD of STING	It can resist HCV infection	[79]
	2'3'-cGAMP	Yes	It has a greater affinity than cGAMP to bind to STING	It can inhibit hepatitis virus infection and alleviate HCC	[78]
	3'3'-cAIMP	Yes	It has stronger binding affinity to STING and can activate all known human STING alleles	It can reduce tumor burden and induce liver inflammation	[71]
	DMXAA	No	It directly binds the CTD of STING	It inhibits HBV replication and aggravates hepatic steatosis and inflammation	[74]
	CMA	No	It directly binds the CTD of STING	It inhibits HBV replication and aggravates hepatic steatosis and inflammation	[73]
Antagonist	Remdesivir	Yes	It can block STING/IRF3 signaling, and the specific mechanism is unknown	It attenuates high-fat diet-induced NAFLD	[84]

STING stimulator of interferon genes, *c-di-AMP* cyclic diadenylate monophosphate, *cGAMP* cyclic GMP-AMP, *cAIMP* cyclic AMP-IMP, *CMA* 10-carboxymethyl-9-acridanone, *DMXAA* 5,6-dimethylxanthenone-4-acetic acid

Conclusion

The effects induced by the activation of STING and its pathway are critical in liver diseases. Although activation of cGAS–STING pathway can resist the invasion of exogenous pathogens in the liver, excessive or abnormal activation of this pathway is detrimental. The ability to treat and prevent liver diseases through the regulation of STING expression is an area that deserves further investigation. MiRNAs inhibit the translation of STING and

reduce its expression level, so whether the exogenous introduction of synthetic miRNAs in hepatocytes can achieve therapeutic effects still needs further investigation. In addition to the identified modulation of STING promoter hypermethylation to treat HBV infection, further analysis is needed to determine whether modulation of STING expression and function by other PTMs can achieve the desired therapeutic effect. Another research area is to further investigate the application of STING agonists and inhibitors in liver diseases. cGAS–STING pathway is a double-edged sword that can be activated or inhibited to achieve the desired effect. For example, in hepatitis virus infection and cancer, stimulation of cGAS–STING pathway can prevent further damage by viral and tumor cells. In contrast, in metabolic liver injury, abnormal activation can lead to exacerbation of the disease. Since liver diseases are not a single existence for progressive occurrence and development, consideration should be given to whether the side effects that arise when activating or inhibiting the pathway interfere with the desired therapeutic effect. Therefore, the use of STING as a target for the treatment of liver disease is of high research value.

Author contributions All authors contributed to the draft and have seen and approved the final version of the report.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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