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REVIEW

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Biological and clinical role of TREM2 in liver diseases

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Abstract

Liver diseases constitute a major health burden worldwide, accounting for more than 4% of all disease-related mortalities. While the incidence of viral hepatitis is expected to decrease, metabolic liver disorders are increasingly diagnosed. Liver pathology is diverse, with functional and molecular alterations in both parenchymal and mesenchymal cells, including immune cells. Triggering receptor expressed on myeloid cells 2 (TREM2) is a transmembrane receptor of the immunoglobulin superfamily and mainly expressed on myeloid cells. Several studies have demonstrated that TREM2 plays a critical role in tissue physiology and various pathological conditions. TREM2 is recognized as being associated with the development of liver diseases by regulating tissue homeostasis and the immune microenvironment. The biological and clinical impact of TREM2 is complex, given its diverse context-dependent functions. This review aims to summarize recent progress in understanding the association between TREM2 and different liver disorders and shed light on the clinical significance of targeting TREM2.

Keywords: liver disease, macrophage, TREM2

INTRODUCTION

Liver diseases are responsible for 2 million deaths each year worldwide, accounting for more than 4% of all disease-related mortalities.[1–4] While the incidence of viral hepatitis is expected to decrease, the prevalence of metabolic and inflammatory liver diseases, including NAFLD and alcohol-associated liver disease, is increasing and becoming a major health burden.[5–7] Liver pathology is diverse, with functional and molecular alterations in both parenchymal and mesenchymal cells, including immune cells. As an important organ for immunity, there are a large number of immune cells that are concentrated in the liver to maintain a homeostatic microenvironment.[8,9] Macrophages represent a key cellular component of the liver immune cells and serve as gatekeepers for initiating or suppressing immune responses as needed. Liver macrophages have been previously classified as tissue-resident KCs and monocyte-derived macrophages (MoMFs). With the

Abbreviations: ALI, acute liver injury; APAP, acetaminophen; DC, dendritic cell; IRI, ischemia-reperfusion injury; LAM, lipid-associated macrophage; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; MoMF, monocyte-derived macrophage; NAM, NASH-associated macrophage; PSC, primary sclerosing cholangitis; SAM, scar-associated macrophage; sTREM2, soluble TREM2; TREM2, triggering receptor expressed on myeloid cells 2

Ke Ma and Shouliang Guo contributed equally.

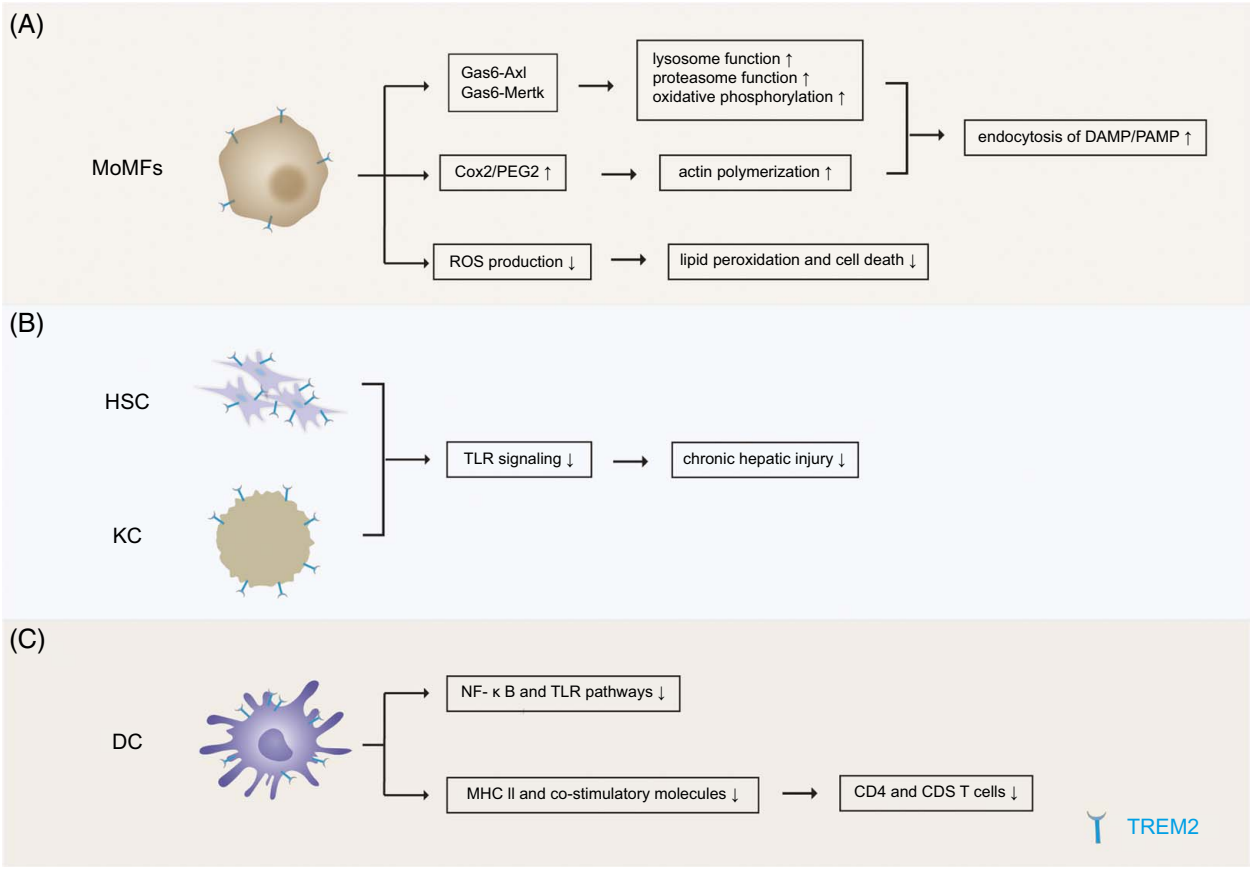

FIGURE 1 TREM2 in liver injury. A. TREM2+ MoMFs in liver injury. B. TREM2+ HSC and TREM2+ KC in liver injury. C. TREM2+ DC in liver injury. Abbreviations: DAMP, damage-associated molecular pattern; MoMF, monocyte-derived macrophage; PAMP, pathogen-associated molecular pattern; ROS, reactive oxygen species; TLR, Toll-like receptor; TREM2, triggering receptor expressed on myeloid cells 2.

development of single-cell and spatial transcriptomic profiling techniques, an underappreciated heterogeneity of liver macrophages has been revealed, and an increasing number of studies have defined distinct macrophage populations with their own unique nomenclature.[10–12]

Triggering receptor expressed on myeloid cells 2 (TREM2) is a transmembrane receptor of the immunoglobulin superfamily, which is mainly expressed on immune cells, particularly myeloid cells.[13] While TREM2 is barely detectable in the majority of tissues under physiological state, its expression significantly increases when tissue damage occurs.[14] Besides MoMFs, TREM2 can be upregulated on tissue-specific macrophages in response to stress, such as microglia in the brain,[15,16] Schwann cells in the peripheral nervous system,[17] osteoblasts in bone,[16] and KCs in the liver.[18] In addition, it has also been found to be expressed in senescence-like neutrophils,[19] dendritic cells (DCs),[20] HSCs,[18,21] and hepatocytes.[22]

Single-cell RNA-seq has been used to profile the macrophages in a wide range of pathologies, and TREM2$^+$ cells represent a notable macrophage subpopulation.[14,23] For example, macrophages in breast cancer have been categorized into FLOR2$^+$ and TREM2$^+$ subgroups.[24] TREM2$^+$ macrophages, which are predominantly distributed around cancer nests, are associated with the depletion of CD8$^+$ T cells in the tumor microenvironment and promote lung metastasis in breast cancer.[25,26] Similarly, 3 subpopulations of macrophages, including resident, inflammatory, and TREM2 highly expressed (TREM2^{hi}) cells, were identified in cardiovascular disease.[27,28] Gene expression and functional analysis confirmed the role of TREM2^{hi} macrophages in cholesterol metabolism and oxidative phosphorylation. In addition, TREM2^{hi} macrophages display anti-inflammatory activities and improve cardiac repair after ischemia injury.[29] In obesity, single-cell RNA-seq analysis showed a group of lipid-associated macrophages (LAMs) that control metabolic homeostasis in a TREM2-dependent manner. LAMs are mainly derived from circulating monocytes under obese conditions and are found around enlarged adipocytes. TREM2 in LAMs drives a gene expression program involving phagocytosis, lipid catabolism, and energy metabolism.[26,30,31] Similarly, TREM2$^+$ macrophages also accumulate in the liver under various stress and injury and play important roles in disease pathogenesis and progression through modulating tissue immune and metabolic homeostasis.

TREM2 IN LIVER INJURY

Acute liver injury (ALI) is characterized by abrupt damage of liver cells that can progress to a fatal outcome within days or weeks. The etiologies of ALI are complex, with the 2 most common being DILI and ischemia-reperfusion injury (IRI).[32]

DILI results from an adverse reaction to drugs or other exogenous substances, leading to unintentional damage of hepatocytes and other nonparenchymal cells. A typical example of DILI is acetaminophen (APAP) hepatotoxicity, which can often lead to liver failure in severe cases.[33] Single-cell RNA-seq analysis identified a reparative macrophage population, MΦ3, that highly expressed TREM2 and peaked 48 hours after APAP-induced ALI, exerting a protective effect (Figure 1A).[34] Bone marrow–derived ly6C^{hi} monocytes infiltrate the injured liver, upregulate pro-restorative wound-healing genes, including TREM2, and differentiate into MΦ3 after 24 hours of APAP-ALI.[35,36] TREM2 on these infiltrating MoMFs inhibits reactive oxygen species production and thereby limits reactive oxygen species-mediated lipid peroxidation and cell death.[21,37] Furthermore, restorative MΦ3 macrophages modulate efferocytosis through autocrine signaling, primarily through the Gas6-Axl and Gas6-Mertk pathways. Genes related to phagosome activity, such as those involved in the lysosome, proteasome, and oxidative phosphorylation functions, are highly expressed in MΦ3, and the phagocytosis of damage-associated molecular patterns and pathogen-associated molecular patterns by MΦ3 is essential for resolving APAP-ALI.[34] Additional studies have shown that TREM2$^+$ MΦ3 is consistent with scar-associated macrophages (SAMs)[38] in fibrotic livers and tumor-associated macrophages[39] in HCC microenvironment.[34] TREM2 can also be induced by pathogen-associated molecular patterns in HSC and KC during liver injury, which dampens Toll-like receptor (TLR4)-mediated inflammation and attenuates chronic hepatic injury (Figure 1B).[21] Overall, the combined effect of liver-infiltrating and resident cells is required for TREM2 to protect the liver from hepatocellular damage, thus acting as a natural brake on inflammation during ALI.

IRI is a common cause of liver damage during surgical procedures such as liver resection and hepatic transplantation, often leading to graft dysfunction. The signaling events leading to hepatocyte injury are complex and involve interactions among hepatocytes, KCs, DCs, LSECs, HSCs, macrophages, neutrophils, and platelets.[40–42] Research on IRI has shown that TREM2 is predominantly expressed in nonparenchymal cells of the liver, particularly DCs, followed by macrophages, which differs from other liver diseases (Figure 1C). In DCs, after acting on TREM2, lipopolysaccharide inhibits the NF-κB and TLR pathways through DAP12 (transmembrane adapter of TREM2[43]), with a reduction of MHC II and costimulatory molecules and proinflammatory factors, and blunts the proliferation and activation of CD4$^+$ and CD8$^+$ T cells, thereby protecting the liver from injury.[20] However, another study that focused on macrophages reported contrasting results. While increased injury in TREM2 knockout mice was observed shortly after IRI, TREM2 knockdown protects the liver against damage at a late stage,[44] which contrasts with the previously noted anti-inflammatory effects of TREM2.[45] Nonetheless, TREM2$^+$ macrophages play an anti-inflammatory role in the resolution of liver IRI inflammation. Myeloid TREM2 is involved in the recognition and internalization of IRI-accumulated apoptotic cells by controlling Rac1-associated actin polymerization through the COX2/PEG2 axis.[44] Thus, TREM2 participates in the inflammatory cascade of IRI in a bipartite manner, with complex and heterogeneous roles at different stages.

In ALI, TREM2$^+$ macrophages or other immune cells quickly accumulate in the liver and mediate response to tissue stress. Given the multifaceted functional impact of TREM2 on myeloid cells, such as phagocytosis, inflammatory and anti-inflammatory cytokine production, and interaction with other cellular compartments, TREM2$^+$ cells likely play diverse roles in distinct types of injury or different stages of disease. In particular, TREM2$^+$ macrophages could affect response to injury and tissue repair in a stage-dependent manner. These complex conditions should be taken into account in the development of therapeutic interventions targeting TREM2 for ALI.

TREM2 IN CHOLESTASIS

Bile flow is driven by the osmotic pressure of solutes secreted by the parietal membranes of hepatocytes and bile duct epithelial cells. When the function of the pumps that secrete these solutes at the cell surface is impaired, an obstruction to flow known as cholestasis occurs, which can lead to liver injury. The most common causes of cholestasis are primary biliary cholangitis and primary sclerosing cholangitis (PSC).[46]

TREM2 expression was upregulated in the livers of patients with primary biliary cholangitis and PSC and positively correlates with markers of disease progression (Figure 2). In the early stages of mouse cholestasis, TREM2 is significantly upregulated and predominantly expressed in KCs and HSCs. The anti-inflammatory receptor TREM2 blunts TLR4-mediated signaling and protects the liver from cholestasis-induced injury. Consistently, TREM2 ablation leads to increased inflammatory response, enhanced necroptotic cell death, and exacerbated biliary expansion in mice with experimental cholestasis, while overexpression of TREM2 in the liver attenuates disease progression by downregulating IL-33 expression and neutrophil

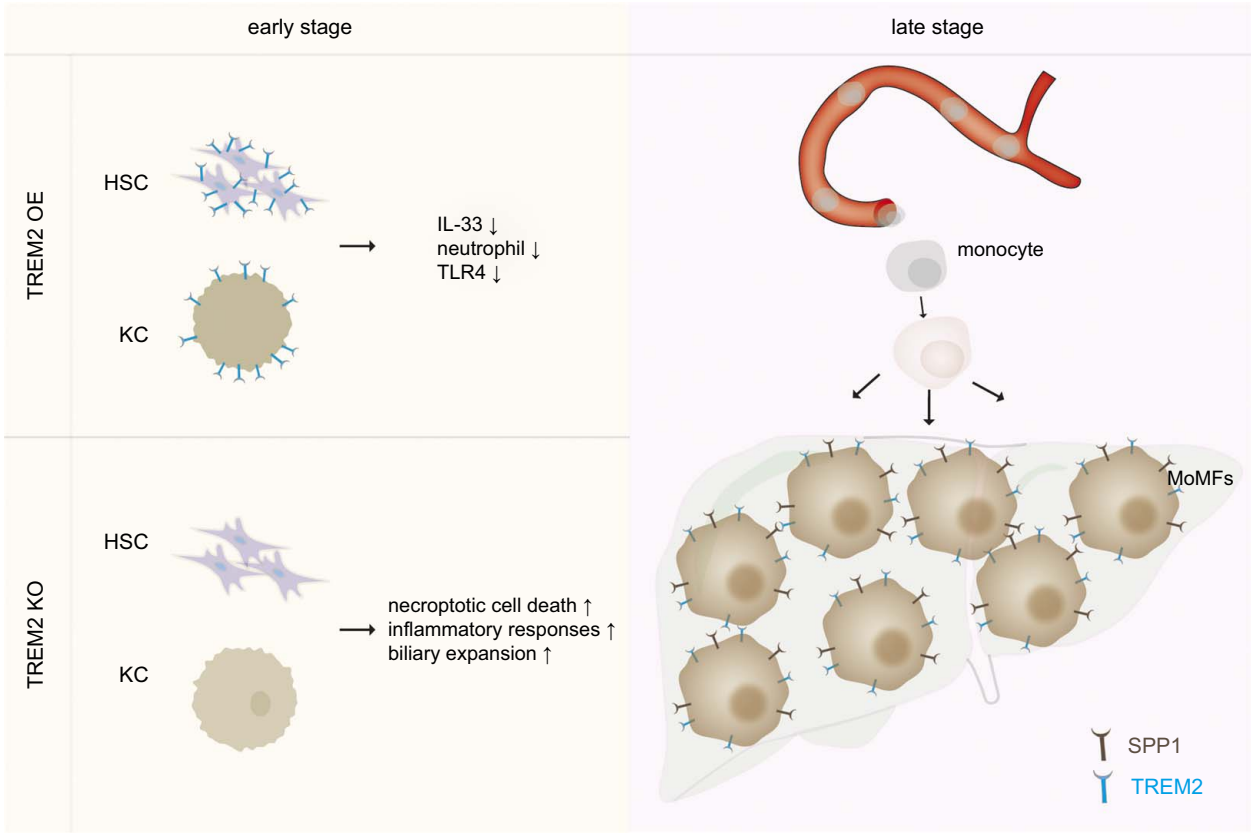

FIGURE 2 TREM2 in cholestasis. Abbreviations: MoMF, monocyte-derived macrophage; TLR4, Toll-like receptor; TREM2, triggering receptor expressed on myeloid cells 2.

recruitment. Ursodeoxycholic acid, a drug commonly used to treat cholestasis, modulates lipopolysaccharide-induced inflammatory injury in a TREM2-dependent manner.[18] As fibrotic cholangitis develops, the percentage of resident KCs decreases, and MoMFs, characterized by osteopontin (Spp1) and Trem2 expression, expand in the liver. MoMFs accumulate around fibrotic regions in both the experimental cholestasis model and human PSC, and their proinflammatory functions are inhibited.[47] In a word, TREM2 acts as a negative regulator of inflammation during cholestasis, representing a novel potential therapeutic target. Future studies investigating the differential effects of HSC-, KC-, and MoMF-specific TREM2 ablation or agonism in experimental PSC will be of interest.

TREM2 IN METABOLIC DISEASES OF LIVER

Metabolic dysfunction–associated steatotic liver disease

NAFLD is the hepatic component of a group of conditions associated with metabolic dysfunction. It has rapidly become the most common chronic liver disease worldwide and is currently estimated to affect up to 38% of the global adult population. In 2023, 3 major multinational liver associations proposed that metabolic dysfunction–associated steatotic liver disease (MASLD) should replace the term NAFLD.[6,48]

Total TREM2 expression and the number of TREM2$^+$ KCs in MASLD donors and a mouse MASLD model are significantly elevated compared with controls and positively correlated with histological analysis.[49–51] Mitofusin2 is a critical hub for the control of mitochondrial fusion, which is required for oxidative phosphorylation, mitochondrial DNA biogenesis, mitophagy regulation, and metabolic adaptation.[52] TREM2 regulates the number and content of macrophage-derived exosomes (Exos) and reduces the amount of miR-106b-5p, which blocks mitofusin2 in hepatocytes. TREM2 knockout impairs antigen processing and presentation, mitochondrial oxidative phosphorylation, and ATP synthesis in KCs while upregulating the expression of genes associated with chemotaxis and inflammation (Ccr2, Cx3cr1, and Spp1). TREM2 deficiency also impairs macrophage-hepatocyte metabolic coordination in a fatty acid–enriched microenvironment and accelerates MASLD progression.[50,51] It should also be noted that the anti-inflammatory effects of TREM2-positive macrophages are equally crucial for preventing MASLD progression. TREM2 controls the triglyceride-rich lipoprotein–induced

proinflammatory response and regulates KC-dependent uptake of apoptotic cells, which is one of the factors leading to the generation of a proinflammatory environment.[53] Furthermore, TREM2 plays a protective role in defense against MASLD-associated sepsis by facilitating long-chain fatty acid oxidation metabolism in the liver. TREM2 deficiency accelerates the initial progression of MASLD and subsequent susceptibility to sepsis, whereas elevated TREM2 gene dosage in liver macrophages suppresses the development of steatohepatitis and ameliorates sepsis-induced organ dysfunction.[51]

Metabolic dysfunction–associated steatohepatitis

NASH is an inflammatory subtype of MASLD, characterized by inflammation, steatosis, and hepatocyte injury (ballooning), with or without fibrosis. Although clinically silent, NASH can progress to cirrhosis, end-stage liver disease, or necessitate liver transplantation.[54] In 2023, the term metabolic dysfunction–associated steatohepatitis (MASH) was chosen to replace NASH.[48]

The role of TREM2 in MASH is more complex and diverse. Extracellular lipid droplets released from injured hepatocytes revitalize TREM2, leading to the emergence of NASH-associated macrophages (NAMs), which are characterized by high expression of TREM2 and glycoprotein nonmetastatic melanoma protein b (GPNMB).[55] TREM2 serves as a marker for identifying at-risk steatohepatitis and is associated with the severity of steatosis, inflammation, hepatocyte ballooning, and liver fibrosis. NAMs are highly responsive to pharmacological and dietary interventions.[56,57] Gene ontology analysis showed that NAMs are enriched for genes involved in endocytosis, lysosomal degradation, MHC II antigen presentation, and extracellular matrix remodeling.[56] Nevertheless, lipid droplets also induce MS4A7-dependent activation of NLRP3 inflammatory signaling, suggesting an unexpected proinflammatory role of NAM.[55] In addition, MASH-induced changes in collaborative transcription factors result in altered binding and function of LXRs, promoting a specific SAM phenotype, which is characterized by increased expression of TREM2 and CD9 and is located in close proximity to areas of fibrosis. SAMs are mainly derived from embryonic KC or recruited CD11b^{lo}F4/80^{hi} macrophages and are associated with tissue scarring in MASH.[38,58] LAMs, which have been previously mentioned, are also found in MASH.[26,59–61] LAMs are located around enlarged adipocytes and highly express lipid-associated signatures. Vertical sleeve gastrectomy has shown clear benefits in improving MASH, with LAMs mediating the vertical sleeve gastrectomy–induced reversal of MASH by repressing inflammation and facilitating efferocytosis in a TREM2-dependent manner. Notably, TREM2 deficiency abolished the protective effects of vertical sleeve gastrectomy, providing evidence that LAMs mediate the beneficial effects of bariatric surgery on MASH.[30,58,62]

Notably, western blotting revealed that although TREM2 level is increased in the early stage of MASLD, it is significantly reduced in MASH. Further studies indicated that the reduction of TREM2 occurs mainly at the protein level rather than at the mRNA level. Hepatocyte-derived S1P upregulates TREM2 in infiltrating liver macrophages, whereas TNF and IL-1β induce TREM2 proteolytic cleavage by activating ADAM17, which impairs macrophage-dependent efferocytosis of lipid-laden apoptotic hepatocytes.[63,64] As described in detail above, we can propose that the expression of TREM2 is inflammation-dependent. Mild inflammation in MASLD status can stimulate TREM2 expression, which plays a key role by promoting phagocytosis and blocking the release of endogenous proinflammatory danger signals. As the increased rate of hepatocyte apoptosis may eventually outcompete phagocyte efferocytosis efficacy, increased inflammatory storms cause reduced TREM2 macrophages.

It is noteworthy that circulating soluble TREM2 (sTREM2) levels are elevated in MASH in both mice and humans. Matching plasma concentrations of sTREM2 with traditional liver disease–associated parameters such as ALT and AST revealed that sTREM2 corresponds to a MASH risk status.[65,66] Criteria for the exclusion and diagnosis of MASH have been proposed (Table 1): a plasma sTREM2 level $\leq$38 ng/mL is an optimal MASH rule-out cutoff (sensitivity 90% and specificity 52%), whereas a plasma sTREM2 level of $\geq$65 ng/mL is an optimal MASH rule-in cutoff (specificity 89% and sensitivity 54%).[67] These results suggested that plasma sTREM2 is a plausible biomarker that may reduce the need for liver biopsies and identify patients eligible for clinical trials in MASH.

TABLE 1 Criteria for the exclusion and diagnosis of MASH

sTREM2	Sensitivity (%)	Specificity (%)	Reference
Rule-in cutoff ($\geq$65 ng/mL)	89	54	[67]
Rule-out cutoff ($\leq$38 ng/mL)	90	52	
Rule-in cutoff ($\geq$986 pg/mL)	56.5	92.9	[66]

Abbreviations: MASH, metabolic dysfunction–associated steatohepatitis; sTREM2, soluble triggering receptor expressed on myeloid cells 2.

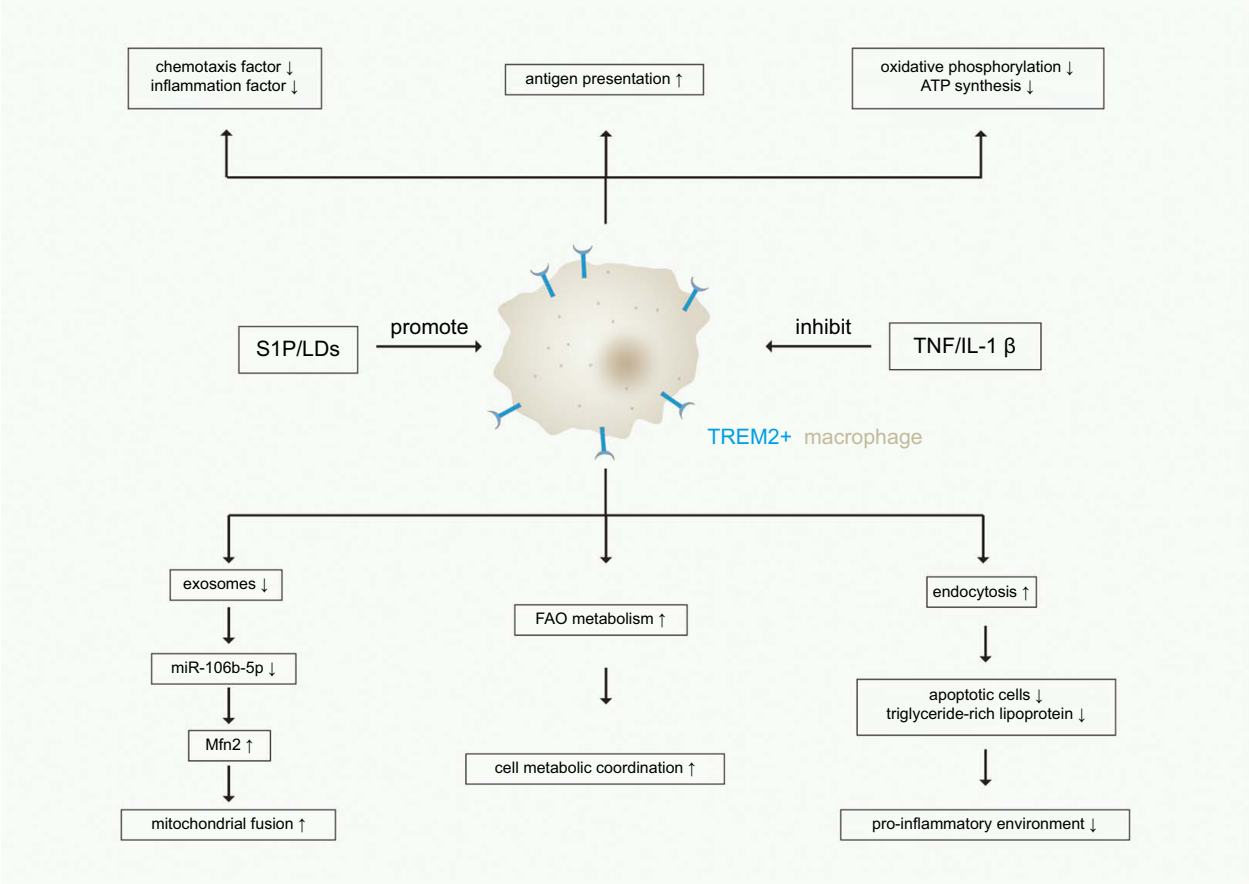

FIGURE 3 TREM2 in metabolic diseases of the liver. Abbreviations: LD, lipid droplet; TREM2, triggering receptor expressed on myeloid cells 2.

In particular, sTREM2 plays an important biological role. It has been reported that sTREM2 has differential effects on cytokine expression in macrophages, with more stimulatory effects on M0 macrophages, and some inhibitory effects on M1 macrophages at early time points, mainly through MAPK-JNK signaling pathways.[68] Unfortunately, there is a lack of in vivo experiments to corroborate these findings.

Given TREM2's involvement in inflammation, lipid metabolism, and efferocytosis (Figure 3), it is a potential therapeutic target for both MASLD and MASH. Modulating TREM2 activity could help control disease progression by altering macrophage function and the immune response.

TREM2 IN LIVER FIBROSIS AND CIRRHOSIS

Liver cirrhosis is prevalent worldwide and is responsible for approximately one million deaths each year. It can result from several causes, including obesity, high alcohol consumption, NAFLD, hepatitis B or C infection, autoimmune diseases, biliary diseases, and iron or copper overload.[3]

The scar-associated TREM2+CD9+ subpopulation of macrophages (SAMs) has been shown to expand during liver fibrosis and differentiate from circulating monocytes (Figure 4). These specific macrophages display a hybrid phenotype with features of both tissue monocytes and KCs.[38] Consistently, mRNA expression analysis using an nCounter gene expression assay showed higher expression levels of representative markers of SAMs, including TREM2, CD68, and CD9 in advanced fibrosis.[69] Flow cytometry confirmed the expansion of TREM2+CD9+ macrophages with a representative expression of matrix metalloproteinase in human fibrotic livers, which can promote fibrillar collagen expression by HSC, indicating that SAMs have a profibrotic phenotype in a matrix metalloproteinase–dependent manner.[38,70,71] Further analysis shows that SAMs are predominantly localized in collagen-positive scar regions, and several populations were identified. The SPP1+ GPNMB+ FABP5+ subpopulation (Fab5) is the most upregulated SAM in human liver fibrosis. RNA velocity analysis demonstrated that monocytes pass through an inflammatory macrophage state before acquiring the Fab5 phenotype. The type 3 cytokines GM-CSF, IL-17A, and TGF-β can collaboratively induce monocyte-to-SAM differentiation, and Fab5 SAMs

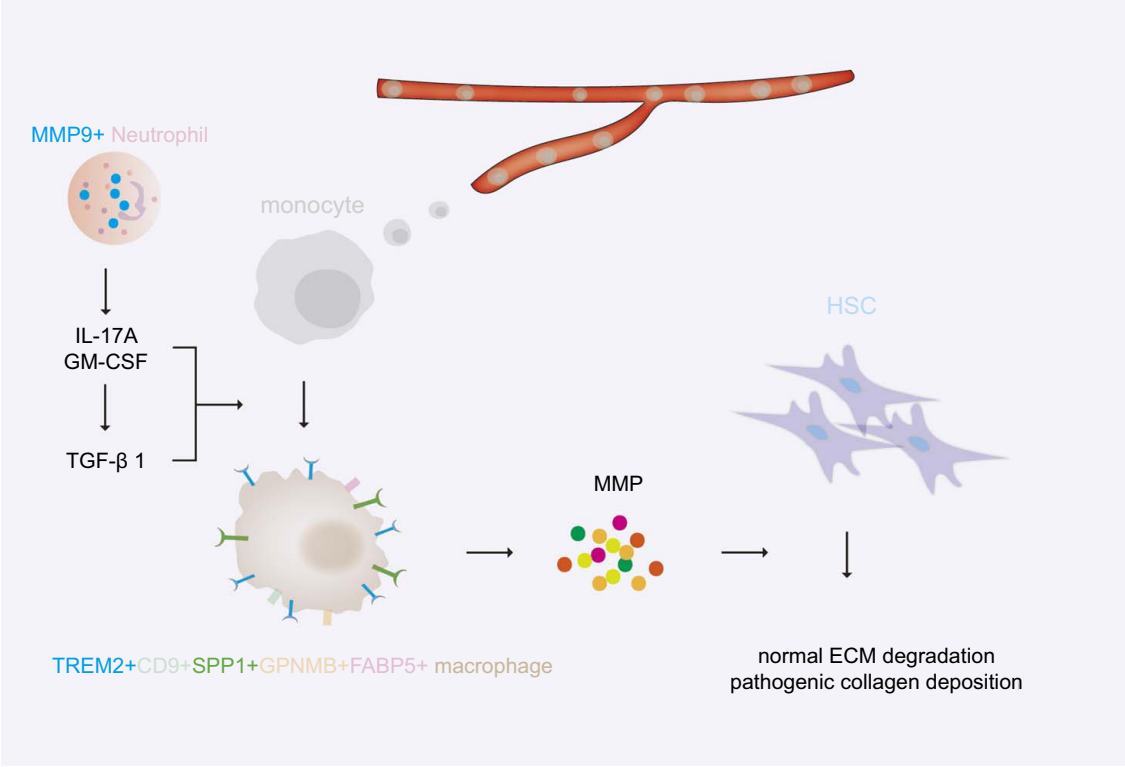

FIGURE 4 TREM2 in liver fibrosis and cirrhosis. Abbreviations: ECM, extracellular matrix; TREM2, triggering receptor expressed on myeloid cells 2.

degrade the normal extracellular matrix and promote pathogenic collagen deposition by mesenchymal cells. Therapeutic TGF-β blockade blunts murine hepatic Fab5 macrophages and fibrosis.[72] Interestingly, another nCounter analysis by Saldarriaga et al[73] showed no significant difference in TREM2 expression among controls, minimal fibrosis, and advanced fibrosis, making the study of TREM2 even more compelling. This discrepancy may be due to the different clinical samples and methods used to assess cirrhosis progression. Taken together, these data suggest that SAMs are monocyte-derived and represent a terminally differentiated cell state within the fibrotic niche that plays a profibrotic role. Future research and clinical trials will be essential to translate these insights into effective treatments for patients.

TREM2 IN LIVER CANCERS

Liver cancer is a major global health challenge and is estimated to affect more than one million individuals annually by 2025. HCC is the most common primary liver cancer and is associated with the presence of chronic liver disease. Major risk factors of HCC include chronic hepatitis infection, aflatoxin B1 exposure, excessive alcohol consumption, MASLD, and liver cirrhosis.[74,75]

TREM2 is significantly upregulated in human HCC and is prominently expressed in tumor-infiltrating macrophages, correlating with markers of inflammation and fibrosis.[76,77] With high CD9 expression, TREM2 macrophages play a protective role by attenuating oxidative stress, inflammation, and hepatocyte damage during the early phases of liver tumorigenesis, and are strongly associated with disease prognosis.[77–79] Overexpression of TREM2 modulates Wnt ligand secretion and reduces HCC tumorigenicity.[77] Interestingly, TREM2 is also expressed in HCC cells and inhibits tumorigenesis and lung metastasis. HCC cell–expressed TREM2 inhibits epithelial-to-mesenchymal transition and mediates oncogenic inhibition through the PI3K/Akt/β-catenin signaling pathway. However, although Tang and colleagues also supported the role of TREM2 as a cancer inhibitor, their work showed significant downregulation of TREM2 by miR-31-5p in HCC. Immunohistochemistry analysis verified that TREM2 expression gradually decreased in the following order: nontumor livers, primary tumors, and metastatic tumors.[22] Differences in the HCC type or stage of development may explain these conflicting results.

However, accumulating evidence suggests an important role of TREM2 in promoting an immune-suppressive tumor microenvironment in cancer.[80–85] In the development of HCC, the hypoxic microenvironment triggers the differentiation of TREM2$^+$ macrophages into the M2 phenotype through the CCL15-CCR1 axis,

which promotes the formation of an immunosuppressive microenvironment and facilitates immune evasion by tumor cells.[86] Furthermore, TREM2$^+$ tumor-associated macrophages suppress the infiltration of CD8+ T cells by low production of CXCL9 and enhance secretion of GAL-1, which promotes PD-L1 overexpression in vessel endothelial cells. CellPhoneDB analysis shows that TREM2 can also recruit regulatory T cells (Tregs) through the CCL20/CXCL9/CXCL10/CXCL12-CXCR3 axes and interact with CD4+ T cells through immune-related ligands and receptors (CD40LG:CD40 and CD28:CD86). Consistently, TREM2 deficiency attenuates HCC tumor growth and improves the efficacy of anti-PD-L1 therapy in these studies, which consider TREM2 as a risk factor.[23,39,87–92]

The role of TREM2 in HCC is too complex to simply categorize it as a cancer-promoting or cancer-suppressing molecule (Figure 5). Considering that the expression levels of TREM2 in tumors vary among different patients with HCC, comparing the outcomes of patients with different levels of TREM2 expression may be a meaningful task.

CONCLUSIONS AND FUTURE PERSPECTIVES

Recent findings have identified the TREM2 receptor as a major immune signaling hub in the pathological state. As sequencing technology has become more widely available, the mystery of TREM2 in liver disease is being unraveled (Figure 6 and Table 2). Although some studies have reported TREM2 expression in hepatocytes, the general consensus is that TREM2 expression is restricted to nonparenchymal cells and plays an anti-inflammatory role in liver diseases. When exposed to stimuli such as injury or infection, the body initiates an inflammatory network, and TREM2 is primarily responsible for limiting inflammatory overgrowth that leads to a storm of inflammatory factors. It is normally expressed in tissue-resident myeloid cells early in the stimulus or during milder periods of stimulation. However, with the depletion of resident cells and increased inflammation, KCs are gradually consumed, and MoMF replaces resident cells as the main population expressing TREM2. As inflammation progresses, TNF and IL-1β are gradually released, resulting in the cleavage of the TREM2 protein by ADAM17. This explains the increase in mRNA levels but a decrease in protein levels, which is often accompanied by an increase in circulating sTREM2.

In liver disease, TREM2 functions mainly through the following aspects: (i) inhibition of inflammatory pathways leading to reduced release of proinflammatory factors; (ii) maintenance of mitochondrial function and normal metabolism; (iii) promotion of fibrillar collagen expression; (iv) enhancement of the phagocytic effect to remove damage-associated molecular patterns/

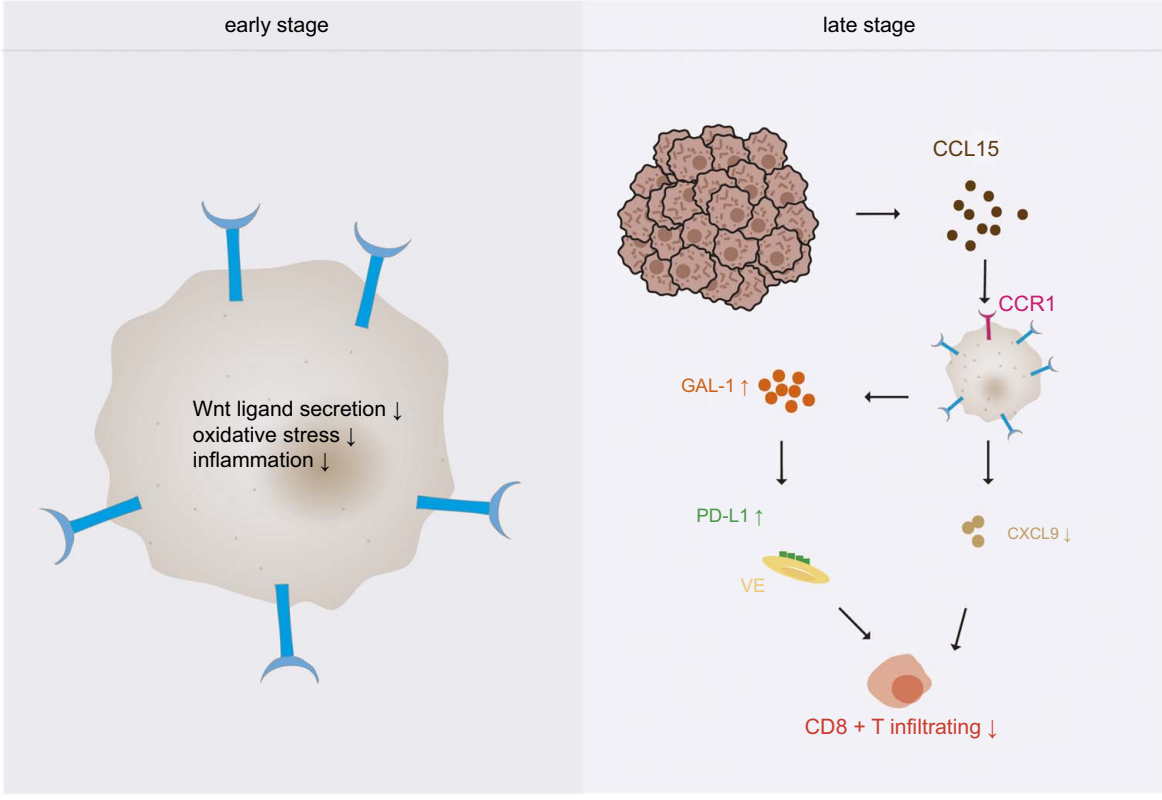

FIGURE 5 TREM2 in liver cancers. Abbreviation: TREM2, triggering receptor expressed on myeloid cells 2.

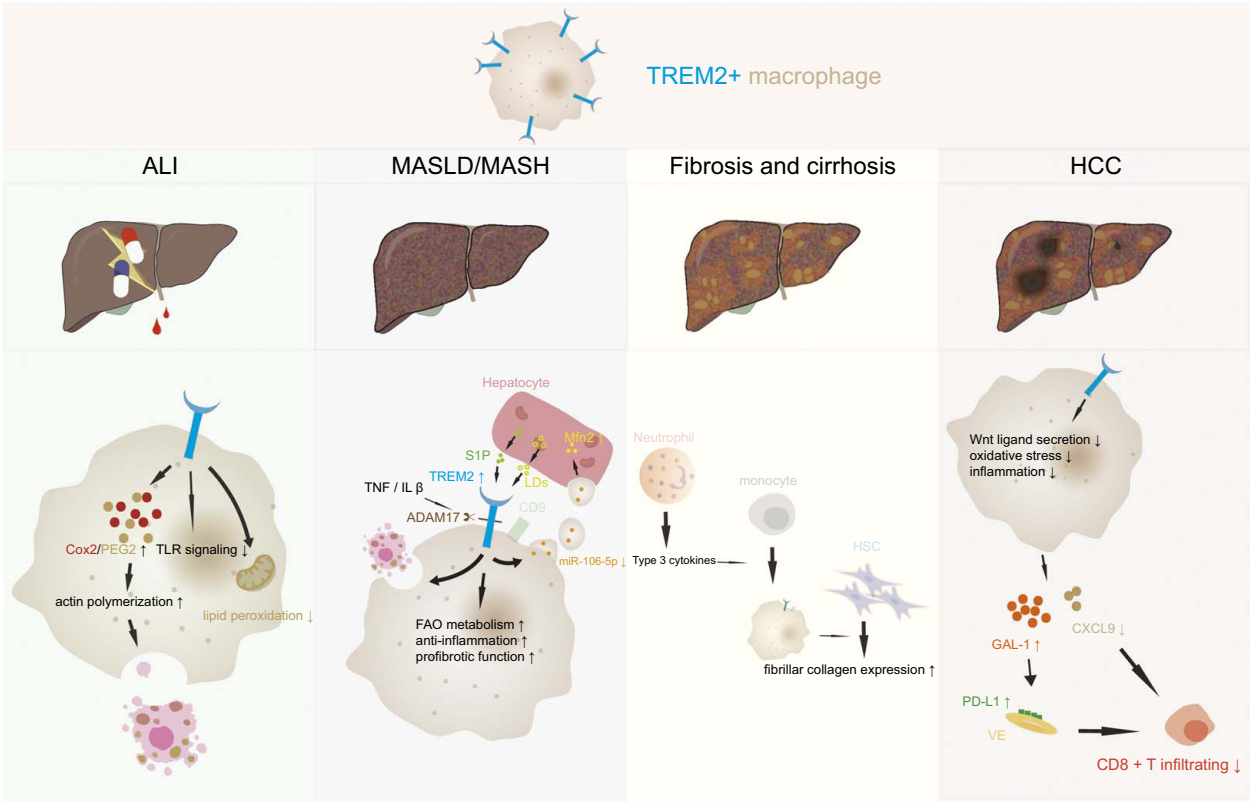

FIGURE 6 Biological and clinical role of TREM2 in liver diseases. Abbreviations: ALI, acute liver injury; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; TREM2, triggering receptor expressed on myeloid cells 2.

TABLE 2 Biological and clinical role of TREM2 in liver diseases

Disease	Mechanism	Cell	Reference
DILI	Limit lipid peroxidation and cell death Promote endocytosis of DAMP/PAMP	MoMFs	[21,34,37]
	Dampen TLR signaling	HSC/KC	[21]
IRI	Dampen TLR and NF-κB signaling Inhibit T-cell activation	DC	[20]
	Promote endocytosis	MoMFs	[44]
Cholestasis	Downregulate IL-33 expression Inhibit neutrophil recruitment Dampen TLR-mediated signaling	KC/HSC	[18]
	Dampen inflammatory responses	MoMFs	[47]
MASLD	Regulate exosomes and endocytosis Blunt inflammatory responses Facilitate FAO metabolism	KC/MoMFs	[50–53]
NASH	Facilitate endocytosis Blunt inflammatory responses Promote ECM remodeling	NAM/LAM/SAM	[55–58,62]
Cirrhosis	Promote fibrillar collagen expression	SAM	[38,69–72]
Cancer	Inhibit tumorigenesis	Hepatocyte	[22]
	Reduce hepatocyte damage Inhibit HCC tumourigenicity	KC/MoMFs	[77–79]
	Hamper T-cell migration	TAM	[39,76,86,89]

Abbreviations: DAMP, damage-associated molecular pattern; DC, dendritic cell; ECM, extracellular matrix; FAO, fatty acid oxidation; LAM, lipid-associated macrophage; MASLD, metabolic dysfunction–associated steatotic liver disease; MoMFs, monocyte-derived macrophages; NAM, NASH-associated macrophage; PAMP, pathogen-associated molecular pattern; SAM, scar-associated macrophage; TAM, tumor-associated macrophage; TLR, Toll-like receptor.

pathogen-associated molecular patterns; and (v) inhibition of the function of T cells. It suggests that TREM2 could be a valuable target for therapeutic intervention in liver disease. Appropriately enhancing or blocking its function according to its role at different stages of liver diseases may be of great benefit to the prognosis. In particular, more attention should be given to SAM, which has been mentioned several times in liver disease. Although SAMs share marker expression with LAMs and NAMs, evidence suggests that SAM occurs regardless of lipid accumulation and in multiple tissues, irrespective of obesity or NASH status. Thus, whether SAMs, LAMs, and NAMs belong to the same group of cells is still highly controversial.

Further research is needed to investigate the function of TREM2 in other live diseases, such as alcoholic liver disease, infectious diseases, and liver metastasis. However, when studying the specific characteristics of TREM2 in liver disease, there are indeed some opportunities and challenges: (1) Technological limitations: There is a lack of recognized effective antibodies against TREM2. Although many teams have verified the presence of TREM2 using different techniques, different antibodies show different results, such as different histochemical positions and inconsistent band positions of western blot, making some studies unreliable. (2) A lack of clinically targeted drugs for TREM2: Ensuring that TREM2-targeted therapies specifically affect TREM2 without unintended effects on other tissues is critical for clinical efficacy and safety. Precision targeting will be essential to avoid off-target effects and potential side effects. Unfortunately, the clinical availability of drugs that specifically block TREM2 is barren. (3) Insufficient clinical evidence: Most of the intervention experiments remain at the mouse level, with studies on human beings more descriptive, primarily through single-cell sequencing. In addition, there is a lack of research on the correlation between TREM2 expression levels and the prognosis of various complex liver diseases. To address these challenges, there is an urgent need to engineer more specific antibodies and clinical drugs that target TREM2 more specifically, which will facilitate comprehensive investigations of TREM2 in pathological states, shedding light on its connection to the onset and progression of liver disease.

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

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