

# Immune Microenvironment on the Molecular Mechanisms and Therapeutic Targets of MAFLD

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**Abstract:** Metabolic dysfunction-associated fatty liver disease (MAFLD) is one of the most prevalent chronic liver diseases worldwide. It is characterized by hepatic steatosis in the absence of significant alcohol consumption, and can progress to liver fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC). Despite its widespread impact, treatment options remain limited, and effective therapies targeting the underlying disease mechanisms are lacking. Recent studies have highlighted the critical role of the liver's immune microenvironment in the onset and progression of MAFLD. However, research into immune-based therapies remains in its early stages. Most existing studies have focused on understanding the immune mechanisms involved, but specific immune targets and therapeutic strategies have yet to be fully explored. This gap has hindered the development of targeted immunotherapies for MAFLD. This review aims to examine the molecular mechanisms of the immune microenvironment in MAFLD and identify potential therapeutic targets, offering insights for future clinical and scientific advancements.

**Keywords:** MAFLD, immune microenvironment, pathway, therapeutic targets

Metabolic dysfunction-associated fatty liver disease (MAFLD), characterized by liver steatosis, is one of the most prevalent chronic liver diseases globally.<sup>1</sup> The disease was redefined in 2023, with the name changing from non-alcoholic fatty liver disease (NAFLD) to MAFLD. This change was made to better reflect the link between metabolic dysfunction and fatty liver disease, a relationship that was not fully captured by the previous term.<sup>2,3</sup> MAFLD's incidence is rising rapidly, with recent epidemiological data projecting a global prevalence of over 30% by 2025. In the United States, the number of affected individuals is expected to reach 27 million by the 2030s, with approximately half of these patients likely to develop significant liver fibrosis.<sup>4</sup> The Asia-Pacific region, particularly mainland China and India, is considered the epicenter of MAFLD, with both high and increasing prevalence rates.<sup>5-7</sup> The pathogenesis of MAFLD is complex, involving factors such as hepatic stellate cell reprogramming, hepatocyte-endothelial interactions, alterations in the liver's immune environment, remodeling of the hepatic microvascular and interstitial environments, and disruptions in metabolic homeostasis.<sup>8,9</sup>

We conducted literature searches using two databases: PubMed (“metabolic associated fatty liver disease” OR “MAFLD”) AND (“immune” OR “immune system” OR “inflammation” OR “immune response” OR “immune pathways” OR “immune-based interventions”), and Web of Science TS=(“metabolic associated fatty liver disease” OR “MAFLD”) AND TS=(“immune” OR “immune system” OR “inflammation” OR “immune response” OR “immune pathways” OR “immune-based interventions”). The search was limited to the past 10 years, yielding a total of 775 documents. We then systematically reviewed the potential mechanisms that contribute to or inhibit the development of MAFLD, with a focus on immune microenvironment-related research targets. Specifically, we examined their key regulatory roles, associated molecular pathways, and potential therapeutic strategies. This review aims to provide strategic insights for future MAFLD therapies, particularly by identifying underexplored targets, mechanisms, and directions for drug development in both clinical and scientific contexts.

## Mechanistic Insights in MAFLD

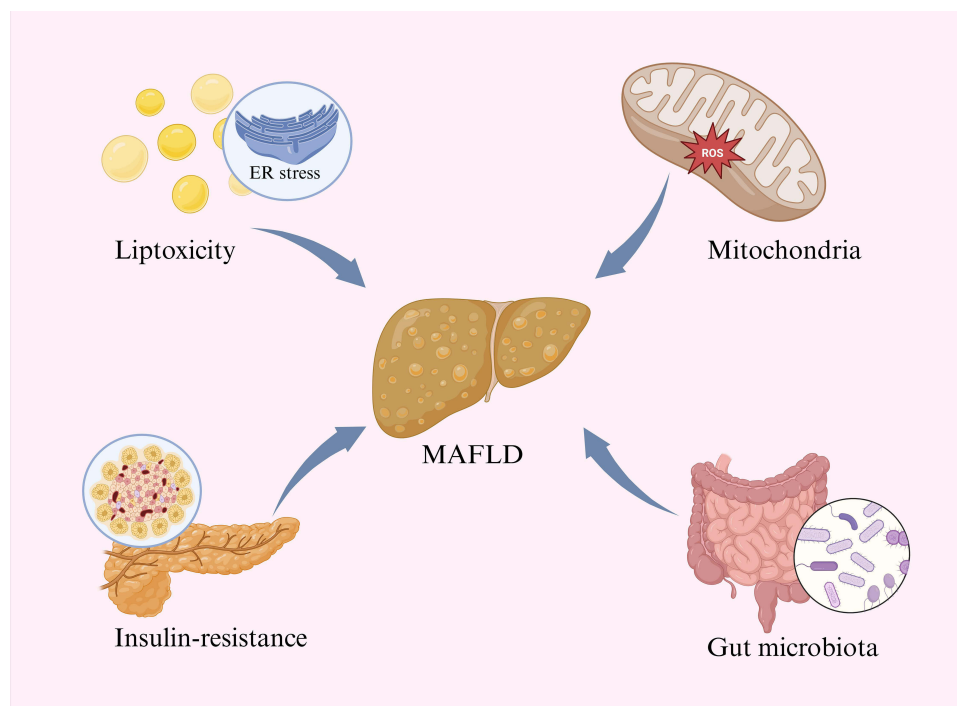
The pathological mechanisms of MAFLD are multifaceted, involving lipid metabolism disorders, oxidative stress, granuloma dysfunction, insulin resistance, and inflammatory responses. Additionally, factors such as intestinal flora imbalances and endoplasmic reticulum stress play significant roles in the disease's progression (Figure 1).<sup>10,11</sup>

In MAFLD, excessive fat accumulation in the liver (hepatic steatosis >5% of liver weight) leads to the oxidation of fatty acids via the beta-oxidation pathway. This process induces endoplasmic reticulum (ER) stress, oxidative stress, and activation of Kupffer cells (KCs),<sup>12</sup> which generate large amounts of reactive oxygen species (ROS).<sup>13</sup> Some lipid peroxidation products can activate hepatic stellate cells (HSCs), which, due to their phagocytic activity and expression of NADPH oxidase, fail to efficiently eliminate ROS, thereby exacerbating oxidative stress.<sup>14–16</sup>

Mitochondria are the primary source of reactive oxygen species (ROS),<sup>17</sup> producing approximately 90% of cellular ROS. When mitochondria are damaged, oxidative phosphorylation is impaired, leading to an increase in ROS production. Excess ROS activate mitochondrial quality control (MQC) mechanisms, including biogenesis, fission, fusion, and autophagy.<sup>18</sup> If these processes fail, mitochondrial dysfunction occurs, which may contribute to the progression of MAFLD.<sup>19</sup> Moore et al reported a 40–50% reduction in beta-oxidation in MASH patients, which correlated with increased ROS production in the liver and decreased markers of mitochondrial biogenesis, autophagy, and mitochondrial dynamics (fission and fusion).<sup>20–22</sup>

Insulin resistance (IR) is characterized by decreased insulin sensitivity in the body, liver, and adipose tissues. In the presence of IR, elevated blood glucose levels and gluconeogenesis trigger metabolic disorders and inflammatory responses, which can lead to liver cell damage and fibrosis. Additionally, reduced adiponectin levels in MAFLD increase free fatty acids (FFAs), disrupting the insulin response and further promoting IR, creating a vicious cycle.<sup>23</sup>

Gut microbes play a key role in bile acid metabolism, and dysbiosis can disrupt the composition of bile acids, affecting their interaction with receptors.<sup>24</sup> This imbalance can impair the intestinal barrier, increase permeability, and allow bacterial endotoxins to enter the bloodstream, triggering a systemic inflammatory response.<sup>25,26</sup> At the same time, it activates Kupffer cells in the liver, leading to the production of pro-inflammatory molecules such as trimethylamine

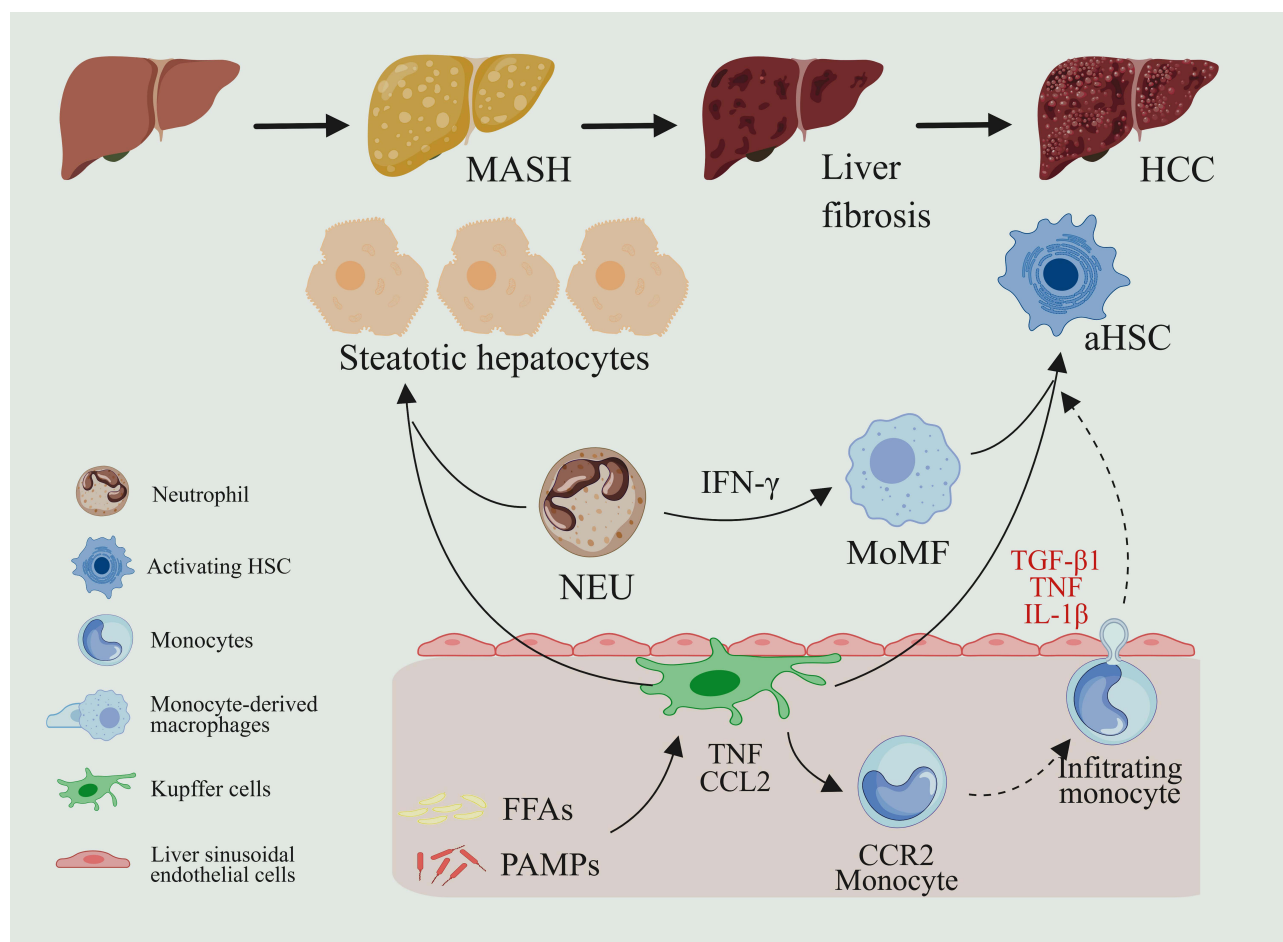


**Figure 1** Fat accumulation can lead to an increase in DNL, FFA and TG. High pressure in the endoplasmic reticulum can lead to the expression of eIF2 $\alpha$ , etc and insulin resistance, mitochondrial damage and intestinal secretion of LPS can all increase the amount of ROS, exacerbate liver inflammation and promote the development of MAFLD. Created in BioRender. Jiang, Z. (2025) <https://BioRender.com/yttgsjt>.

N-oxide (TMAO), secondary bile acids (SBAs), and bacterial 16sDNA.<sup>27,28</sup> These molecules exacerbate liver inflammation and fibrosis, potentially accelerating the progression of MAFLD.<sup>29</sup>

## Liver Immune Microenvironment

Kupffer cells are activated, releasing pro-inflammatory cytokines that trigger inflammatory responses and hepatocellular injury in MAFLD.<sup>30</sup> The reactive oxygen species (ROS) produced by these activated Kupffer cells also promote hepatic stellate cell (HSC) activation. HSCs, in turn, secrete chemokines that recruit monocytes and other immune cells to the liver, exacerbating inflammation.<sup>31</sup> Once activated, HSCs release cytokines and growth factors, such as TGF- $\beta$ ,<sup>32</sup> which further enhance Kupffer cell activity, creating a positive feedback loop that accelerates both MAFLD progression and liver fibrosis.<sup>33</sup> Neutrophils worsen hepatocyte injury and inflammation by secreting elastase, ROS, and various pro-inflammatory cytokines, as well as chemokines like IL-8, which recruit additional immune cells to the liver.<sup>34,35</sup> Natural killer (NK) cells and natural killer T (NKT) cells, which are both pro-inflammatory and cytotoxic, also contribute to disease progression.<sup>36</sup> NKT cells release TNF superfamily member 14 (TNFSF14), which increases free fatty acid (FFA) uptake by hepatocytes, promoting steatosis.<sup>37</sup> Dendritic cells (DCs), as potent antigen-presenting cells, secrete pro-inflammatory cytokines such as IL-12 and TNF- $\alpha$  upon activation, promoting Th1 cell differentiation and enhancing liver inflammation.<sup>38</sup> Finally, dysfunction in liver endothelial cells (LECs), which regulate blood flow and metabolism, may further exacerbate liver injury (Figure 2).<sup>39-41</sup>



**Figure 2** Free fatty acids stimulate Kupffer cells to produce inflammatory factors such as TNF and aggravate liver inflammatory response and injury through NF- $\kappa$ B and JNK signaling pathways, while immune cells such as monocytes, macrophages, and neutrophils promote the activation of HSCs through inflammatory factors such as TGF- $\beta$ 1, TNF, and IL-1 $\beta$ ; on the other hand, Kupffer cells also promote lipid deposition in hepatocytes, further aggravating MAFLD. Created by Medpeer. Zhonghao J (2025) [www.medpeer.cn](http://www.medpeer.cn).

## Immune Microenvironment and Pathways of MAFLD

### Involvement of Intrinsic Immune Cells

As discussed in [Liver Immune Microenvironment](#), innate immune cells play a multifaceted role in MAFLD, contributing to liver cell damage clearance, activation of fibrosis, and regulation of the immune microenvironment balance at various stages of the disease.

### Role of Adaptive Immune Cells

In MAFLD, Th1 and Th17 cells exacerbate liver damage by activating innate immune cells and secreting pro-inflammatory cytokines such as interferon gamma (IFN- $\gamma$ ) and IL-17. Th2 cells produce IL-4 and IL-13, which, under certain conditions, can promote fibrosis.<sup>35,42</sup> In contrast, Tregs secrete IL-10 and TGF- $\beta$ ,<sup>43</sup> which help inhibit inflammation and maintain immune homeostasis. However, in MAFLD, the number and function of Tregs are diminished, leading to worsened inflammation.<sup>30,31,33</sup> Additionally, CD8+ T-cells contribute to MASH by directly attacking liver cells. B cells further aggravate liver fibrosis and inflammation by producing antibodies, activating the complement system, and presenting antigens.

### Release of Pro-Fibrotic Factors

Transforming growth factor-beta (TGF- $\beta$ ) is the primary profibrotic factor driving the progression of MAFLD to fibrosis. It activates hepatic stellate cells (HSCs) and stimulates the synthesis of extracellular matrix (ECM) proteins through the Smad signaling pathway, contributing to fibrosis. Other factors, including platelet-derived growth factor (PDGF), tumor necrosis factor-alpha (TNF- $\alpha$ ), insulin-like growth factor-1 (IGF-1), and endothelin-1 (ET-1), also promote HSC proliferation, migration, and ECM synthesis through various signaling pathways. TNF- $\alpha$  further enhances fibrosis by indirectly inducing other pro-fibrogenic factors, such as TGF- $\beta$  and interleukin-1 $\beta$  (IL-1 $\beta$ ), which worsen inflammation. ET-1 exacerbates the hypoxic environment in the liver through vasoconstriction, further promoting fibrosis. Additionally, chemokines like CCL2 (MCP-1) and stromal cell-derived factor-1 (SDF-1) activate HSCs by attracting monocytes and macrophages to the liver, creating a local inflammatory microenvironment that accelerates fibrosis.<sup>44</sup> These profibrogenic factors form complex molecular networks that drive the progression of fatty liver disease to fibrosis and cirrhosis.<sup>43</sup>

### Effects of Disorders of Lipid Metabolism

In MAFLD, insulin resistance leads to excessive free fatty acid (FFA) accumulation, causing fat buildup in liver cells, triglyceride formation, and the production of toxic substances like malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE),<sup>45</sup> which activate liver immune cells. This also triggers inflammatory pathways, such as toll-like receptor 4 (TLR4), and the release of pro-inflammatory cytokines like TNF- $\alpha$  and IL-6.<sup>46,47</sup> Lipid metabolism disorders and sustained inflammation activate hepatic stellate cells (HSCs), which secrete extracellular matrix components, contributing to liver fibrosis.<sup>48</sup> Additionally, excess lipids impair autophagy and disrupt the intestinal barrier, allowing endotoxins to enter the liver, further promoting inflammation and fibrosis.

### Role of the Gut-Liver Axis

Patients with MAFLD often exhibit imbalances in their intestinal flora, with an increase in harmful bacteria and a decrease in beneficial ones. This disrupts intestinal barrier function, leading to increased permeability and allowing bacterial products and metabolites to enter the bloodstream. These substances are then transported to the liver via the portal vein, where they activate immune cells and trigger an inflammatory response.<sup>49</sup> Additionally, bile acids, short-chain fatty acids (such as butyric acid and propionic acid), and tryptophan derivatives produced by gut microbiota metabolism can directly influence liver metabolism and immune function, thereby modulating inflammation and lipid accumulation.<sup>28</sup>

## Autophagy and Oxidative Stress

Autophagy plays a protective role in MAFLD by reducing ROS production through the removal of damaged mitochondria, thus alleviating oxidative stress.<sup>50,51</sup> It also degrades lipid droplets in hepatocytes (lipophagy), reducing fat accumulation and mitigating hepatic steatosis. Additionally, autophagy exerts an anti-inflammatory effect by clearing necrotic cells and the danger-associated molecular patterns (DAMPs) they release, inhibiting immune activation.<sup>52</sup> However, during MAFLD progression, excessive ROS generated by oxidative stress can impair the autophagy pathway, disrupting its function and worsening oxidative stress in a vicious cycle that accelerates liver damage.<sup>53–55</sup> Therefore, combining antioxidants with autophagy activators may provide a more effective treatment approach for MAFLD, offering improved therapeutic options for patients.

## Remodeling of the Immune Microenvironment

The remodeling of the immune microenvironment is a key factor in the progression of MAFLD. Studies indicate that the immune profile in MAFLD patients differs significantly from that of healthy controls, with notable changes in immune cell subpopulations and cytokine secretion. For example, CD4+ T-cells exhibit abnormal function in MAFLD, and their absence in the liver microenvironment is closely associated with the progression to fibrosis and hepatocellular carcinoma (HCC).  $\gamma\delta$  T-cells also play a crucial role in MAFLD; gut microbiota influence liver inflammation and fibrosis by modulating the activation of these cells.<sup>56</sup> *Akkermansia muciniphila* (Akk bacteria), a beneficial gut bacterium, inhibits the development of MAFLD by regulating the polarization of  $\gamma\delta$  T-cells and macrophages, which not only affects liver inflammation but also influences fibrosis by modulating hepatic stellate cell activation.<sup>57,58</sup>

The interaction between changes in the liver's immune microenvironment and the molecular mechanisms underlying MAFLD drives its progression to MASH, fibrosis, and liver cancer. Additionally, metabolic signaling pathways such as AMPK,<sup>59</sup> mTOR,<sup>59,60</sup> and PI3K/AKT<sup>61</sup> influence immune cells and interact with immune signaling pathways like NF- $\kappa$ B<sup>62,63</sup> and JNK/MAPK,<sup>64,65</sup> collectively regulating inflammation and disease progression in MAFLD<sup>66,67</sup> (Table 1 and Figure 3). Therefore, targeting the liver immune microenvironment through these signaling pathways to inhibit pro-inflammatory factors, modulate immune cell subsets, and improve the gut-liver axis may provide new therapeutic strategies for MAFLD.

## Therapeutic Strategies

### Anti-Dyslipidemia Therapy

Triglyceride transferase 2 (DGAT2) catalyzes triglyceride formation and plays a crucial role in triglyceride accumulation in the liver. A Phase II trial assessed the safety, efficacy, and tolerability of PradiGastat (a DGAT1 inhibitor).<sup>58,72</sup> The results demonstrated that liver fat content was reduced by at least 30% in the high-dose (35.29%) and low-dose (30%) groups, compared to a 10.53% reduction in the placebo group.<sup>73</sup>

Microsomal triglyceride transfer protein (MTTP) plays a critical role in the assembly and secretion of very-low-density lipoprotein (VLDL). Inhibiting MTTP reduces VLDL formation, thereby decreasing liver lipid accumulation.<sup>74</sup>

The TRIM56-FASN axis has also been identified as a potential therapeutic target for MAFLD. Researchers at the University of Science and Technology of China found that TRIM56, an E3 ubiquitin ligase, slows MAFLD progression by promoting the degradation of FASN, a key enzyme involved in fatty acid synthesis.<sup>75</sup>

Farnesoid X receptor (FXR) activation, primarily in hepatocytes and intestinal epithelial cells, inhibits bile acid (BA) synthesis, reduces liver fat production and gluconeogenesis, and prevents liver inflammation, fibrosis, and cell death.<sup>76–78</sup> Obeticholic acid, the first FXR agonist to enter Phase III clinical trials, showed significant promise in lowering liver fat content and improving liver function, though it was not FDA-approved due to efficacy and side effects.<sup>79,80</sup>

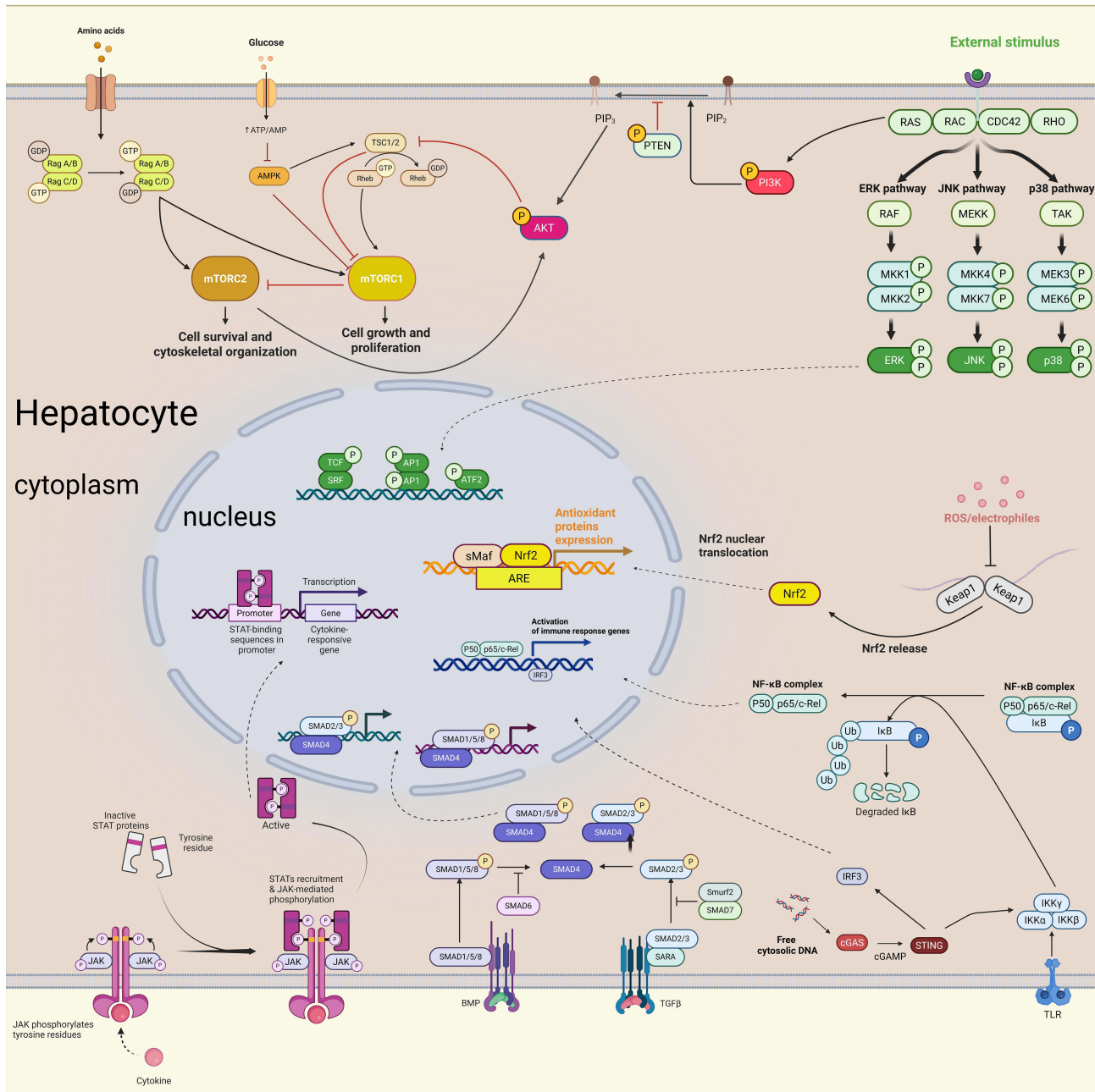
Retinol-binding protein-4 (RBP-4) exacerbates insulin resistance and liver damage by interfering with the insulin signaling pathway, promoting lipogenesis, and activating pro-inflammatory and pro-fibrotic signaling pathways. Inhibiting RBP-4 synthesis or targeting its function with novel delivery systems could provide a new treatment strategy

**Table 1** Relevant Signaling Pathways in and for MAFLD

Signaling Pathway Name	Immune cells Involved	Molecular Targets	Therapeutic Relevance of MAFLD	Reference
<b>NF-κB</b> signaling pathway	Macrophages, T cells, B cells, NK cells, etc.	IKK complex (IKKα, IKKβ, NEMO), p50, RelA, IκB family (IκBα, IκBβ, etc), A20, CYLD, LUBAC	NF-κB is involved in the activation of HSC and promotes a pro-fibrotic HSCs phenotype, promotes the secretion of inflammatory factors (IL-6, IL-1b, and TNF-α), leads to IR, hepatocellular injury, and promotes the progression of MAFLD and MASH.	[60,61]
<b>PI3K/Akt</b> signaling pathway	Macrophages, T cells, B cells, etc.	PI3K (p110α, p110δ, etc), Akt, mTOR, TSC1/2, Bcl-2 family, BCRP	Phosphate and tensin homolog (PTEN) is a negative regulator of the PI3K/Akt pathway that inhibits the expression of hepatic DNL and IR-related enzymes, and deletion of PTEN activates PI3K/AKT, which elevates the levels of SREBP-1c and adipogenic genes and promotes the development of MASH.	[59]
<b>JAK-STAT</b> signaling pathway	Macrophages, T cells, B cells, NK cells, etc.	JAK (Jak1, Jak2, Jak3, Tyk2), STAT (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, STAT6)	Obesity and excess glucose inhibit growth hormone secretion, which disrupts GH/JAK2/STAT5 signaling, leading to excessive hepatic lipid accumulation and promoting the development of MAFLD.	[68]
<b>AMPK</b> signaling pathway	Macrophages, T cells, B cells, etc.	LKB1, CAMKK2, mTORC1, ULK1/hATG1, SIK1, SIK2, MARKs, SADS	AMPK activation reduces apoptosis and oxidative stress, activates autophagy via the LKB1-AMPK-mTOR pathway, and reduces Bax/Bcl-2 expression levels, thereby slowing down MAFLD progression.	[57]
<b>JNK/MAPK</b> signaling pathway	Macrophages, T cells, B cells, NK cells, etc.	RAS family (HRAS, KRAS, NRAS), RAF family (ARAF, BRAF, CRAF), MEK, ERK1/2, JNK, p38 MAPK	Increased FFAs, ROS, and TNF-α lead to JNK activation in hepatocytes and macrophages, which increases inflammatory cytokine production, leading to inflammation, apoptosis, liver injury, and fibrosis, and promotes the development of MAFLD and carcinogenesis.	[62,63]
<b>TGFβ/SMAD</b> signaling pathway	Macrophages, T cells, B cells, HSCs, etc.	TGF-β ligands, TGF-β receptors (TGF-β RI and TGF-β RII), SMADs (SMAD2, SMAD3, SMAD4)	TGF-β acts through the ALK-5 receptor to trigger the SMAD signaling pathway, phosphorylates SMAD 2 and 3 proteins, and forms a trimeric complex with SMAD 4 protein, which enters the nucleus and initiates fibrotic liver disease gene expression.	[30,41]
<b>Nrf2</b> signaling pathway	Macrophages, T cells, B cells, etc.	Nrf2, Keap1, ARE, NAD(P)H, Heme oxygenase-1, Pirin	Nrf2 activation inhibits ROS production, regulates Bcl-2/Bax ratio and PARP cleavage, and reduces apoptosis, thereby slowing down the process of MAFLD.	[69,70]
<b>cGAS-STING</b> signaling pathway	Macrophages, DCs, NK cells, etc.	cGAS, STING, TBK1, IRF3, IFNβ	The cGAS-STING signaling pathway has a dual role in MAFLD, promoting inflammation and fibrosis on the one hand, and playing a protective role by inducing autophagy on the other hand.	[64,65]
<b>mTOR</b> signaling pathway	Macrophages, T cells, B cells, etc.	mTORC1(mTOR, Raptor, PRAS40, MLST8) and mTORC2(mSin1, Protor, DEPTOR)	Aberrant activation or inhibition of the mTOR signaling pathway affects the balance of cellular autophagy, which in turn affects lipid metabolism and inflammatory responses in the liver.	[57,58]

<b>Wnt/β-catenin</b> signaling pathway	Macrophages, T cells, B cells, etc.	Wnt ligands, Frizzled receptors, LRP5/6, β-catenin, TCF/LEF transcription factors	Activation of the Wnt/β-catenin pathway Activation of this pathway promotes hepatic regeneration and improves metabolic function, whereas inhibition of this pathway attenuates hepatic steatosis and inflammation in order to avoid promoting fibrosis or HCC.	[71]
<b>Notch</b> signaling pathway	Macrophages, T cells, B cells, etc.	Notch receptors (Notch1-4), Notch ligands (Jagged1, Jagged2, Delta-like 1, Delta-like 4), CSL transcription factor	The Notch signaling pathway plays a role in regulating liver cell differentiation and bile duct formation In MAFLD. Inhibiting Notch signaling has shown potential in reducing bile duct proliferation and fibrosis.	[42,45]
<b>PPAR</b> signaling pathway	Macrophages, T cells, B cells, etc.	PPARα, PPARγ, RXR	PPARα activation promotes fatty acid oxidation, while PPARγ activation enhances insulin sensitivity and reduces hepatic steatosis. Fibrates (PPARα agonists) and thiazolidinediones (PPARγ agonists) have been used clinically to improve lipid profiles and insulin resistance.	[15,16]

**Abbreviations:** IKK complex, IκB kinase complex; p50, A subunit of the NF-κB transcription factor complex; RelA, A subunit of NF-κB; IκB family: Inhibitors of κB; CYLD, A deubiquitinase that inhibits NF-κB activation; LUBAC, Linear ubiquitin chain assembly complex; PI3K, Phosphoinositide 3-kinase; Akt, protein kinase B (PKB); mTOR, Mammalian target of rapamycin; TSC1/2, Tuberous sclerosis complex 1 and 2; Bcl-2 family, Regulators of apoptosis; BCRP, Breast cancer resistance protein; JAK, Janus kinase family; STAT, Signal transducer and activator of transcription family; LKB1, A serine/threonine kinase; CAMKK2, Calcium/calmodulin-dependent protein kinase kinase 2; mTORC1, Mammalian target of rapamycin complex 1; ULK1/hATG1, Unc-51-like kinase 1; SIK1/SIK2, Salt-inducible kinases; MARKs, Microtubule affinity-regulating kinases. RAS family, Small GTPases; RAF family, Serine/threonine kinases; MEK, Mitogen-activated protein kinase kinase; ERK1/2, Extracellular signal-regulated kinases; JNK, c-Jun N-terminal kinase; p38 MAPK, Mitogen-activated protein kinase; SMADs: Small nuclear proteins; Nrf2, Nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; ARE, Antioxidant response element; NADPH, Nicotinamide adenine dinucleotide phosphate; Heme oxygenase-1, Heme oxygenase 1; cGAS, Cyclic GMP-AMP synthase; STING, Stimulator of interferon genes; TBK1, TANK-binding kinase 1; IRF3, Interferon regulatory factor 3; IFNβ, Interferon beta; mTORC1/2, Mammalian target of rapamycin complex 1/2; Wnt ligands, Wnt family proteins; Frizzled receptors, G protein-coupled receptors for Wnt ligands; LRP5/6, Low-density lipoprotein receptor-related proteins; β-catenin, A key regulatory protein in the pathway; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor transcription factors; PPARα, Peroxisome proliferator-activated receptor alpha; PPARγ, Peroxisome proliferator-activated receptor gamma; RXR, Retinoid X receptor.



**Figure 3** Eight key signaling pathways and related targets affecting the development of MAFLD, as well as providing suitable options for subsequent targeted therapies. Created in BioRender. Jiang, Z. (2025) <https://BioRender.com/5mu5Xru>.

**Abbreviations:** ADAM 10, A member of the ADAM family of proteins; GDP/GTP, Guanosine diphosphate/guanosine triphosphate; AMPK, AMP-activated protein kinase; Rag A/B, Rag C/D, Proteins involved in the regulation of mTORC1 signaling; mTORC1/mTORC2, Mammalian target of rapamycin complex I and complex 2; TSC1/2, Tuberous sclerosis complex 1/2; Rheb, Ras homolog enriched in brain; PI3K, Phosphatidylinositol-3-kinase; PIP<sub>2</sub>/PIP<sub>3</sub>, Phosphatidylinositol-4,5-bisphosphate/phosphatidylinositol-3,4,5-trisphosphate; AKT, protein kinase B; PTEN, Phosphatase and tensin homolog; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; AP1, Activator protein 1; ATF2, Activating transcription factor 2; Nrf2, Nuclear factor-erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; ARE, Antioxidant response element; PPAR, Peroxisome proliferator-activated receptor; RXR, Retinoid X receptor; EGFR, Epidermal growth factor receptor; GPCR, G protein-coupled receptor; TNFR, Tumor necrosis factor receptor; IL-1R, Interleukin-1 receptor; BMP, Bone morphogenetic protein; TGFβ, Transforming growth factor beta; TLR, Toll-like receptor; JAK, Janus kinase; STAT, Signal transducer and activator of transcription; SMAD, A family of proteins involved in TGFβ signaling; IKK, IκB kinase; NF-κB, Nuclear factor kappa-B; IRF3, Interferon regulatory factor 3; STING, Stimulator of interferon genes; cGAS, Cyclic GMP-AMP synthase; cGAMP, Cyclic GMP - AMP.

for MAFLD.<sup>81</sup> Additionally, circulating RBP-4 levels correlate with MAFLD severity and may serve as an early biomarker for high-risk patients. Researchers at Peking University proposed the “Fibrotic Overexpression and Retention (FORT)” strategy, using mRNA lipid nanoparticles (LNPs) to deliver therapeutic proteins directly to liver

lesions. This method leverages the high expression of RBP-4 in fibrotic livers, enhancing protein retention and efficacy for precise liver fibrosis treatment.<sup>69,70</sup>

Osteocalcin (OCN) regulates fatty acid uptake through the AMPK-FOXO1/BCL6-CD36 signaling pathway, reduces liver lipid accumulation, activates the Nrf2 pathway to combat oxidative stress,<sup>68,82</sup> inhibits the JNK pathway to mitigate inflammation,<sup>64,83</sup> and improves insulin resistance, thereby regulating glucose and lipid metabolism.<sup>84</sup> In clinical studies, chemically synthesized osteocalcin (csOCN) has been shown to alleviate liver damage in MAFLD mouse models by reducing fatty acid uptake via CD36 regulation.

## Anti-Inflammatory Treatment

Chemokine receptors CCR2/CCR5 mediate the recruitment of monocytes and macrophages, which release pro-inflammatory factors that promote liver inflammation and fibrosis.<sup>85</sup> Berberine (BBR) has been shown to improve MAFLD by modulating the chemokine/CMKLR1 signaling pathway, thereby reducing liver inflammation and lipid deposition.<sup>86</sup>

High-mobility group box 1 protein (HMGB1) activates pro-inflammatory responses through the HMGB1/RAGE signaling pathway, contributing to liver damage.<sup>87</sup> A novel RG-I pectin-like polysaccharide, YJ3A1, purified from roses, may inhibit MAFLD progression by suppressing the expression and release of HMGB1.<sup>88</sup>

Cyclooxygenase-2 (COX-2), a key enzyme in the production of prostaglandin E2 (PGE2), activates inflammatory pathways, including NF- $\kappa$ B and PI3K-AKT, through its receptors (EP1-4). This promotes the release of pro-inflammatory factors such as TNF- $\alpha$  and IL-6, exacerbating liver inflammation.<sup>89</sup> Inhibitors of the COX-2/PGE2 axis could provide more comprehensive metabolic improvements in MAFLD patients.<sup>90</sup>

NLRP3 inflammasomes contribute to MAFLD progression by activating inflammation, inducing oxidative stress, and regulating lipid metabolism.<sup>91</sup> Inhibitors such as MCC950 and OLT1177 reduce the release of inflammatory factors (eg, IL-1 $\beta$  and IL-18) by blocking NLRP3 activation, alleviating liver inflammation and fibrosis.<sup>71</sup>

Mitochondrial antiviral signaling protein (MAVS) plays a critical role in mitochondrial function, protecting cells from metabolic stress by interacting with the VDAC2 protein on the outer mitochondrial membrane. In MAFLD models, the absence of MAVS exacerbates mitochondrial dysfunction, leading to increased fat accumulation and heightened inflammatory responses. MAVS also regulates lipid metabolism pathways, reducing liver fat production and accumulation.<sup>92</sup>

## Antifibrotic Therapy

The PDGF, NLRP3-caspase-1, and Wnt/ $\beta$ -catenin signaling pathways are key regulators of HSC activation and fibrogenic progression in MAFLD.<sup>93</sup> Targeting these pathways may inhibit HSC activation and mitigate liver fibrosis.<sup>94</sup> For instance, PDGF receptor inhibitors such as imatinib have demonstrated promising results in liver fibrosis models.<sup>95</sup>

Lysyl oxidase-like protein 2 (LOXL2) catalyzes the cross-linking of collagen, enhancing the stability and stiffness of the extracellular matrix (ECM) and promoting liver fibrosis. Consequently, the LOXL2 inhibitor simtuzumab represents a potential new treatment for MAFLD.<sup>96</sup>

ASK1 inhibitors, such as GS-4997, reduce oxidative stress, inhibit inflammatory responses, and block ASK1-mediated p38 and JNK signaling pathways, leading to decreased stellate cell activation.<sup>97</sup> These inhibitors have shown significant anti-fibrotic and anti-inflammatory effects in MAFLD treatment.<sup>98</sup>

Galectin-3 is a crucial mediator in liver fibrosis and inflammation. Inhibitors like GR-MD-02 can reduce stellate cell activation and collagen deposition, thereby alleviating fibrosis. Combining such treatments with FXR agonists or immune checkpoint inhibitors could further enhance their anti-fibrotic and anti-inflammatory effects.<sup>99,100</sup>

## Immunomodulation

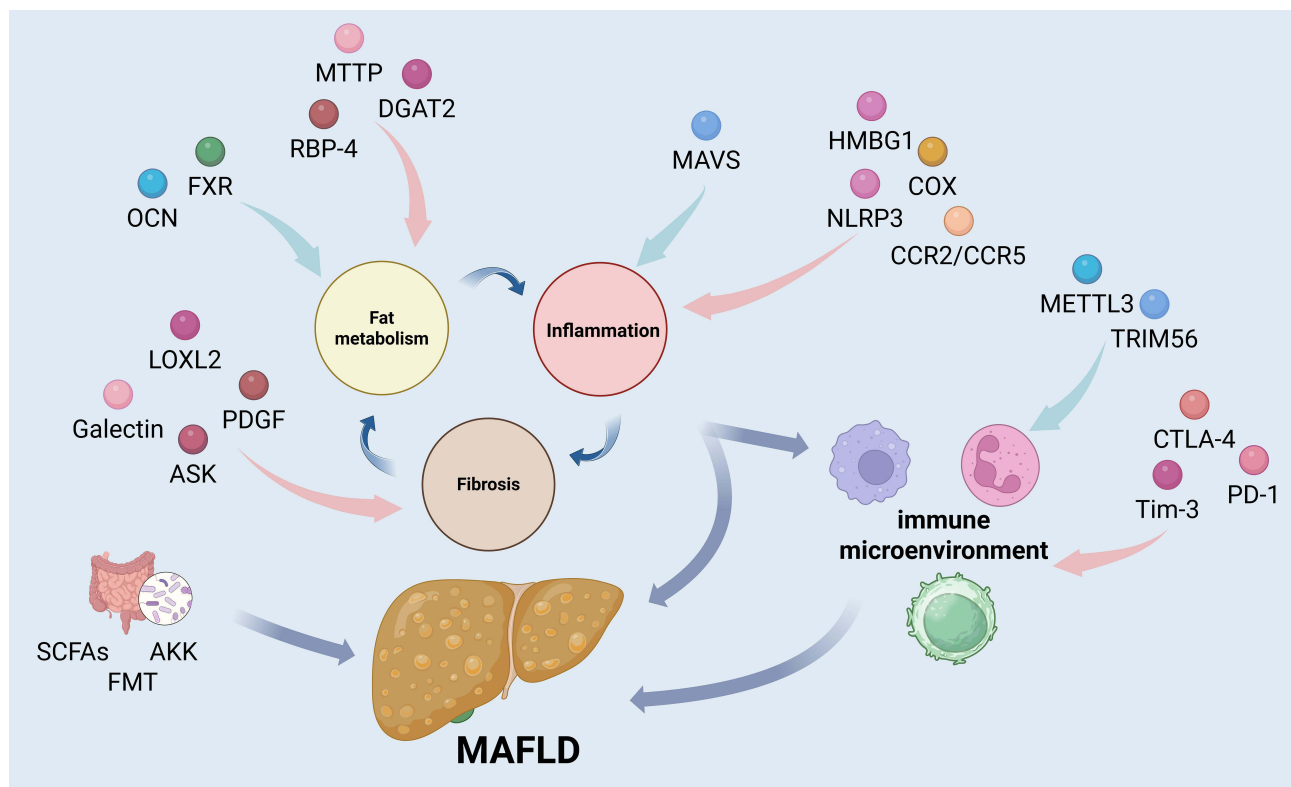
Immunological checkpoint molecules such as CTLA-4, PD-1/PD-L1, and Tim-3 play essential roles in regulating immune responses. Inhibiting these checkpoints can enhance the immune system's ability to detect and clear liver lesions. For example, PD-1 inhibitors like pembrolizumab have demonstrated potential efficacy in clinical studies of MAFLD.<sup>101–103</sup>

Additionally, the m6A methyltransferase METTL3, which has been identified as a potential therapeutic target for MAFLD-associated hepatocellular carcinoma (MAFLD-HCC),<sup>104</sup> promotes cholesterol biosynthesis by modulating m6A-modified SCAP. This, in turn, affects the function of CD8<sup>+</sup> T-cells within the tumor microenvironment, thereby enhancing anti-tumor responses.<sup>105</sup>

## Intestinal Flora

*Akkermansia muciniphila* (Akk bacteria) enhances immune function, reduces inflammation, and improves both intestinal immunity and metabolism.<sup>106</sup> Probiotics, such as *Bifidobacteria* and *Lactobacilli*, along with short-chain fatty acids (SCFAs), have been shown to decrease the production of inflammatory factors.<sup>107</sup> Fecal microbiota transplantation (FMT), which involves transplanting healthy gut flora, helps restore intestinal microecology.<sup>108</sup> These approaches have demonstrated promise in clinical trials and offer novel strategies for treating MAFLD.

Targeted therapies also contribute to improving the immune microenvironment in MAFLD through various mechanisms. These include inhibiting adipogenesis, promoting the oxidative breakdown of fat, regulating macrophage subpopulations, enhancing T-cell function, suppressing immunosuppressive cells, reducing the release of inflammatory factors, and modulating the gut microbiome (Figure 4). Together, these mechanisms open up new therapeutic targets and treatment strategies for MAFLD.



**Figure 4** Relevant targets (red for promotion, blue for inhibition) affect MAFLD either directly by influencing lipid metabolism, inflammation, and fibrosis or by acting on the immune microenvironment. Created in BioRender: Jiang, Z. (2025) <https://BioRender.com/6t6ta22>.

**Abbreviations:** MTTP, Microsomal Triglyceride Transfer Protein; DGAT2, Diacylglycerol O-acyltransferase 2; RBP-4, Retinol-binding protein 4; FXR, Farnesoid X Receptor; OCN, Osteocalcin; MAVS, Mitochondrial Antiviral Signaling Protein; HMBG1, High Mobility Group Box 1; COX, Cyclooxygenase; NLRP3, NLR Family Pyrin Domain Containing 3; CCR2/CCR5, Chemokine receptors key for immune cell chemotaxis and migration; LOXL2, Lysyl Oxidase Like 2; Galectin, A family of proteins binding carbohydrates; PDGF, Platelet-Derived Growth Factor, a multifunctional cytokine; ASK, Apoptosis Signal-Regulating Kinase; METTL3, Methyltransferase-Like 3; TRIM56, Tripartite Motif Containing 56; CTLA-4, Cytotoxic T-Lymphocyte Associated Protein 4; Tim-3, T-cell Immune Receptor with Ig and ITIM Domains; PD-1, Programmed Cell Death Protein 1; SCFAs, Short-Chain Fatty Acids; AKK, *Akkermansia*; FMT, Fecal Microbiota Transplantation.

## Conclusion and Outlook

MAFLD is a global chronic liver disease with a complex pathogenesis involving multiple factors such as lipid accumulation, insulin resistance, and oxidative stress. A decade-long analysis of the immune microenvironment in MAFLD reveals that imbalances in immune cell subpopulations, abnormal activation of immune pathways, and disrupted immune-metabolic interactions play key roles in its development and progression. However, research into immune-based therapeutic interventions remains limited.

Currently, the US Food and Drug Administration (FDA) has not approved any drugs specifically for the treatment of simple fatty liver disease or MAFLD. Ongoing clinical trials, such as the Phase III trials of Rezdiffra by Madrigal Pharmaceuticals, Aramchol by Galmed Pharmaceuticals, and Semaglutide by Novo Nordisk, primarily focus on metabolic targets, with few studies targeting immune regulation.

Though some immunomodulatory treatments have shown promise in animal studies—such as FGF-21 therapy, which reduces liver fat and improves insulin resistance—questions remain about their long-term effects on inflammation and fibrosis, their interaction with immune cells, and their efficacy across varying metabolic states. CCR2/CCR5 inhibitors, like ceniciviroc, have improved insulin resistance in mouse models, but large-scale clinical trials are necessary for validation.

Adoptive cell therapies targeting immune cells such as Tregs and NKT cells show limited clinical progress, with small sample sizes and low-quality evidence. Immune checkpoint inhibitors (ICIs) hold promise in MAFLD-associated hepatocellular carcinoma (MAFLD-HCC), but the evidence is still limited. Similarly, while dietary fiber supplementation has shown potential to improve gut microbiota and regulate immune responses, studies have been small and lack long-term follow-up.

To establish effective immunotherapies for MAFLD, large-scale, multicenter clinical trials are essential. These should aim to validate the efficacy and safety of immunomodulatory drugs, precisely target affected areas, minimize systemic immunosuppression, reduce adverse reactions, and optimize treatment regimens.

Future studies should focus on investigating the dynamic changes and interactions of various immune cell subpopulations (eg, different T-cell types and macrophage subpopulations) at different stages of MAFLD, such as simple steatohepatitis, MASH, and liver fibrosis. These studies should aim to clarify the specific mechanisms by which these cells contribute to disease progression and identify early diagnostic markers and prognostic indicators that reflect immune microenvironmental reorganization. By detecting changes in immune cell subpopulations, cytokines, chemokines, and other biomarkers in blood or liver tissue, we can enable precise assessment of MAFLD disease status and develop personalized treatment plans.

For instance, lipid-associated macrophages (LAMs) gradually replace resident Kupffer cells during MAFLD progression. These LAMs activate hepatic stellate cells by secreting factors like SPP1, promoting liver fibrosis. Additionally, studying how metabolic products such as fatty acids and bile acids in the local liver microenvironment influence immune cell activity, differentiation, and function—and vice versa—could provide insights into the complex interplay between metabolism and immunity in MAFLD.

Strengthening interdisciplinary collaboration and integrating advanced technologies like genomics and metabolomics will allow for a more comprehensive assessment of the immune status and disease progression in MAFLD patients. This approach could also enable the exploration of combined treatment strategies, such as combining immunotherapy with anti-inflammatory therapies, metabolic regulation, and anti-fibrotic treatments, to synergistically improve the immune microenvironment and enhance treatment efficacy.

Moreover, targeted therapies that focus on specific immune cell subpopulations or signaling pathways, combined with lifestyle interventions (eg, dietary control and exercise), and interventions aimed at modulating the gut microbiota (eg, probiotics, prebiotics, and fecal microbiota transplantation), may provide novel therapeutic strategies to treat MAFLD.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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