



Review Article



Myeloid-derived Suppressor Cells in Metabolic Dysfunction-associated Fatty Liver Disease

Guozirui Mou^{1#}, Jingnan Xiong^{1#}, Liyuan Chen^{1#}, Manni Tan¹, Yina Ma¹, Taduoji Ze², Xia Li¹ and Hongyun Zhao^{1*} 

¹Department of Gastroenterology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China; ²The First Department of Internal Medicine, The People's Hospital of Qamdo, Qamdo, Tibet Autonomous Region, China

Received: June 02, 2026 | Revised: June 29, 2026 | Accepted: September 11, 2026 | Published online: October 29, 2026

Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) has become a rapidly increasing global health concern, driven by metabolic stress, chronic inflammation, and progressive fibrotic remodeling. Myeloid-derived suppressor cells (MDSCs) have emerged as pivotal yet context-dependent modulators of MAFLD pathogenesis. This review summarizes the biological characteristics of MDSCs, their immunosuppressive mechanisms, and their multifaceted roles in MAFLD progression, including hepatic steatosis, chronic inflammation, and fibrogenesis. Quantitative synthesis reveals that murine models demonstrate MDSC expansion (~3-fold with a high-fat diet, $P < 0.05$) and suppression of MDSC-associated proinflammatory mediators (e.g., MitoTEMPO reduced hepatic S100A8 mRNA by 5.9-fold, $P < 0.001$). In one human cohort ($n = 98$), hepatic CD33+/HLA-DR- MDSC density correlated with inflammation grade (Spearman $r = 0.610$, $P < 0.001$) and fibrosis stage ($r = 0.687$, $P < 0.001$), though this cross-sectional dataset lacked MAFLD-specific stratification and longitudinal validation. We further discuss emerging MDSC-targeted strategies and explicitly acknowledge current translational gaps. Collectively, this review provides a mechanistic and critically appraised framework positioning MDSCs as both promising therapeutic targets and potential biomarkers for MAFLD.

Citation of this article: Mou G, Xiong J, Chen L, Tan M, Ma Y, Ze T, et al. Myeloid-derived Suppressor Cells in Metabolic Dysfunction-associated Fatty Liver Disease. J Clin Transl Hepatol 2026. doi: 10.14218/JCTH.2026.00396.

Introduction

With the ongoing transformation of modern lifestyles and dietary habits, metabolic dysfunction-associated fatty liver disease (MAFLD),^{1,2} also widely referred to as nonalcoholic

fatty liver disease (NAFLD),³ has become the most prevalent chronic liver disorder worldwide. It is now recognized as a major contributor to progressive liver injury, including cirrhosis and hepatocellular carcinoma, and affects the health of hundreds of millions of individuals globally. MAFLD affects approximately 30% of the global population, with rising prevalence in China and worldwide.^{1,2} This growing burden underscores the urgent need to identify novel immunometabolic drivers of disease progression.

MDSCs are a heterogeneous population of immunosuppressive myeloid cells that represent precursors of dendritic cells (DCs), macrophages (Mφ), and/or granulocytes. These cells have emerged as important regulators in a wide range of pathological conditions, including cancer, chronic infection, autoimmune disorders, and chronic metabolic disease.⁴ By inhibiting both innate and adaptive immune responses, MDSCs are increasingly recognized as pivotal modulators of inflammatory microenvironments and tissue remodeling.

The identification of MDSCs has provided a new perspective on immune regulation during liver disease progression. However, their precise role in MAFLD remains incompletely understood. This review therefore aims to summarize the current understanding of the biological functions and mechanistic roles of MDSCs in MAFLD, with particular emphasis on how MDSC-mediated immune regulation contributes to disease initiation and progression. In addition, we discuss the potential of MDSCs as therapeutic targets and highlight how interventions directed at MDSC-dependent immunoregulatory pathways may offer new opportunities for precision treatment of MAFLD.

Despite accumulating evidence from murine models, several critical gaps remain: (i) whether MDSC subsets identified in mice are phenotypically conserved in human MAFLD; (ii) the lack of validated circulating MDSC biomarkers for disease staging; and (iii) the safety concerns surrounding MDSC-targeted therapies in metabolic diseases. This review critically appraises current evidence, explicitly addresses these translational hurdles, and highlights subset-specific functions that may inform precision therapeutics.

Overview of MAFLD

MAFLD is closely associated with obesity, type 2 diabetes mellitus, hypertension, and related metabolic disorders. Its disease spectrum encompasses metabolic dysfunction-associated fatty liver (MAFL) and metabolic dysfunction-associated

Keywords: Myeloid-derived suppressor cells; MAFLD; MASH; Hepatic inflammation; Liver fibrosis; Immunometabolism.

*Contributed equally to this work.

*Correspondence to: Hongyun Zhao, Department of Gastroenterology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China. ORCID: <https://orcid.org/0009-0004-5824-3707>. Tel: +86-13527464949, E-mail: zhychina@cqmu.edu.cn.

ated steatohepatitis (MASH), as well as progressive hepatic fibrosis and cirrhosis.^{5,6} The pathogenesis of MAFLD has not yet been fully elucidated, and the currently prevailing framework is the “multiple-hit hypothesis”.⁷ The initial insult is centered on hepatic lipid metabolic imbalance, characterized by increased lipogenesis, elevated free fatty acids, and insulin resistance, all of which promote hepatic lipid accumulation. Subsequent hits, including oxidative stress, mitochondrial dysfunction, and activation of inflammatory pathways, act synergistically to induce hepatocellular injury, persistent inflammation, and fibrogenesis, ultimately driving progression toward cirrhosis or hepatocellular carcinoma. Genetic susceptibility and environmental influences also play important roles in MAFLD pathogenesis.⁸ Taken together, MAFLD arises through a multidimensional and multilayered pathogenic process, and clarification of these mechanisms is essential not only for a deeper understanding of disease biology but also for the development of diversified targeted therapeutic strategies.

Immune regulation also plays a pivotal role in MAFLD progression, with multiple immune cell populations contributing to disease progression. T cells promote hepatic stellate cell (HSC) activation through secretion of cytokines such as interleukin-4 (IL-4), interleukin-13 (IL-13), and interleukin-17 (IL-17), thereby enhancing liver fibrogenesis, while simultaneously contributing to hepatocellular injury, metabolic dysregulation, and insulin resistance.^{9,10} Mφ trigger inflammatory responses and liver injury through the release of proinflammatory mediators. Lipotoxic stimulation restricts the self-renewal of Kupffer cells (KCs), while infiltrating bone marrow-derived monocytes differentiate into proinflammatory monocyte-derived macrophages, together exacerbating hepatic injury and fibrosis.^{11,12} DCs infiltrate MASH livers, and their abundance is positively correlated with disease severity. By driving proinflammatory T-cell phenotypic reprogramming, DCs mediate an inflammation–fibrosis cascade that aggravates hepatic pathological injury.¹³ MDSCs, as a heterogeneous population with potent immunosuppressive properties, also participate in MAFLD progression by regulating lipid metabolic disturbances, inflammatory responses, and fibrotic remodeling. Emerging evidence suggests bidirectional crosstalk between MDSCs and KCs: MDSC-derived interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) may suppress KC self-renewal,¹⁴ while activated KCs produce CCL2 that can recruit myeloid cells including MDSCs,¹⁵ potentially establishing a feed-forward loop that perpetuates immune dysregulation.

Biological characteristics of MDSCs

Definition and classification of MDSCs

MDSCs are a highly heterogeneous population composed of myeloid progenitors and immature myeloid cells (IMCs), and they are characterized by potent immunosuppressive activity. Under physiological conditions, IMCs generated in the bone marrow rapidly differentiate into mature granulocytes, Mφ, or DCs, and therefore MDSCs are present only at low levels in healthy individuals. However, under pathological conditions such as cancer, trauma, infectious diseases, and certain autoimmune or chronic inflammatory disorders, the differentiation of IMCs into mature myeloid cells is blocked, resulting in the abnormal expansion of the MDSC compartment.⁴ According to their developmental and phenotypic characteristics, MDSCs are broadly classified into two major subsets: granulocytic MDSCs (G-MDSCs) and monocytic MDSCs (M-MDSCs). It should be noted, however, that the phe-

notypic definition of these populations differs between humans and mice.^{4,16,17} This species-specific difference should be taken into account when interpreting experimental findings and translating them into clinical settings.

Mechanisms of MDSC-mediated immunosuppression

In chronic inflammatory diseases, MDSCs exert profound immunosuppressive effects on both innate and adaptive immune responses, thereby contributing to disease progression. Their suppressive activity is primarily mediated through high expression of arginase-1 (ARG1), inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS), all of which impair T-cell function (Fig. 1).⁴ Among these subsets, G-MDSCs preferentially rely on ROS and ARG1 to mediate immunosuppression and do so largely independently of iNOS, whereas M-MDSCs mainly depend on nitric oxide (NO) as well as immunosuppressive cytokines such as IL-10 and TGF-β (Fig. 1).^{4,18}

MDSCs suppress immune responses through multiple coordinated mechanisms. T helper 2 (Th2)-associated cytokines activate the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, thereby up-regulating ARG1 expression and causing depletion of L-arginine, which in turn inhibits expression of the CD3ζ chain and blocks synthesis of cyclin D3 and cyclin-dependent kinase 4, ultimately impairing T-cell antigen recognition and proliferation.^{18,19} Upon stimulation with T helper 1 (Th1) cytokines, iNOS competes with ARG1 for the common substrate L-arginine and catalyzes the production of NO. NO disrupts T-cell proliferation and differentiation by nitrating the T-cell receptor (TCR), blocking interleukin-2 (IL-2) receptor signaling, and inhibiting the Janus kinase 3–signal transducer and activator of transcription 5 (JAK3-STAT5) pathway.^{4,14} ROS, in turn, directly suppress T-cell function by damaging the CD3ζ chain via H₂O₂ and by mediating ONOO[−]-dependent nitration of the TCR; notably, inhibition of ROS production in MDSCs can almost completely reverse their immunosuppressive activity.^{4,18,20} In addition, MDSCs secrete TGF-β, which down-regulates NKG2D receptor and perforin expression on natural killer (NK) cells, suppresses interferon-γ (IFN-γ) production, and interferes with the antigen-presenting capacity of DCs through oxidized lipids.^{21,22} Together, these synergistic pathways constitute the highly effective immunosuppressive network orchestrated by MDSCs.

Key roles of MDSCs in MAFLD progression

MDSCs regulate immune responses through the secretion of cytokines such as IL-10 and TGF-β, as well as immunomodulatory mediators including ROS, ARG1, and prostaglandin E2 (PGE2). Through dynamic interactions with other immune cell populations, MDSCs promote hepatic lipid accumulation and lipid metabolic dysregulation, while simultaneously sustaining chronic inflammatory responses, accelerating fibrogenesis, and ultimately driving the progression of MAFLD.

MDSCs promote hepatic lipid accumulation and lipid metabolic disturbance

MDSCs contribute to hepatic steatosis through multiple cooperative mechanisms that integrate immune regulation with metabolic remodeling. First, MDSCs secrete immunosuppressive cytokines, including IL-10 and TGF-β. IL-10 negatively regulates M1 polarization of Mφ, reduces inflammatory cell infiltration within the liver, and thereby attenuates immune responses triggered by lipid accumulation.^{14,23} In addition, IL-10 enhances the expansion and suppressive func-

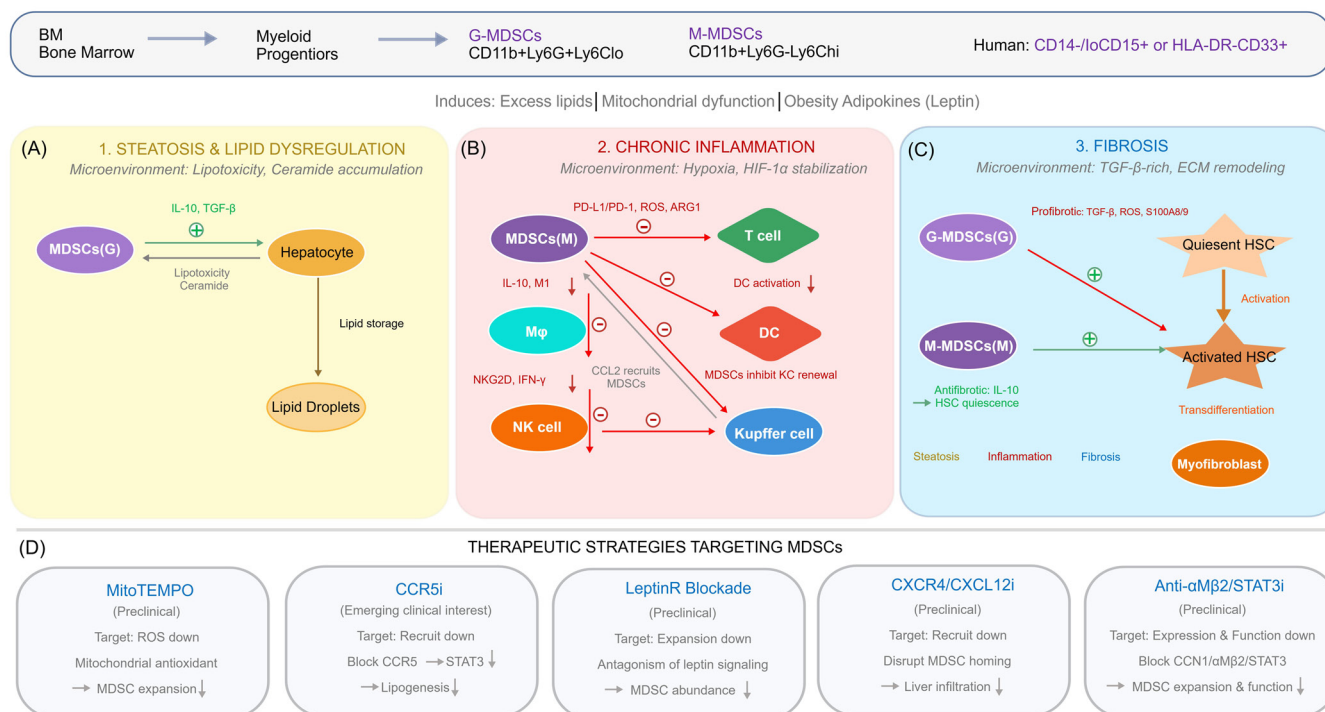


Fig. 1. Mechanistic network of MDSCs in MAFLD progression. Bidirectional cellular interactions between myeloid-derived suppressor cells (MDSCs) and hepatic parenchymal or immune cells across three stages of MAFLD progression, with stage-specific microenvironmental cues and therapeutic targets. (A) Steatosis and lipid dysregulation: granulocytic MDSCs [G-MDSCs (G)] promote hepatocyte lipid storage via interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) (green arrows with ⊕), while lipotoxicity and ceramide released from steatotic hepatocytes reciprocally activate G-MDSCs (grey bidirectional arrow). Hepatocyte-derived lipid accumulation further drives lipid droplet formation. (B) Chronic inflammation: monocytic MDSCs [M-MDSCs (M)] establish an immunosuppressive microenvironment through programmed death ligand-1 (PD-L1)/PD-1 interactions, reactive oxygen species (ROS), and arginase-1 (ARG1), thereby inhibiting T-cell proliferation, macrophage (Mφ) M1 polarization, dendritic cell (DC) activation, and Kupffer cell (KC) self-renewal (dark red arrows with ⊖). TGF-β from MDSCs suppresses natural killer (NK) cell NKG2D receptor expression and interferon-γ (IFN-γ) production. A reciprocal feedback loop is depicted by which activated KCs release CCL2 to recruit additional M-MDSCs into the inflamed liver (green arrow). Microenvironmental drivers include hypoxia and hypoxia-inducible factor-1α (HIF-1α) stabilization. (C) Fibrosis: dual-pathway illustration of MDSC effects on hepatic stellate cells (HSCs). G-MDSCs promote HSC activation and subsequent myofibroblast transdifferentiation via a profibrotic TGF-β/ROS/S100A8/9 pathway (dark red arrow with ⊕), whereas M-MDSCs exert an antifibrotic effect through IL-10-mediated maintenance of HSC quiescence (green arrow with ⊕). The microenvironment is characterized by TGF-β-rich gradients and extracellular matrix (ECM) remodeling. (D) Therapeutic strategies targeting MDSCs in MAFLD. MitoTEMPO (mitochondrial antioxidant) reduces MDSC expansion by lowering ROS. CCR5 inhibition blocks G-MDSC CCR5→STAT3 signaling, reducing recruitment and lipogenesis (emerging clinical interest; early-phase human trials for steatohepatitis ongoing). Leptin receptor blockade antagonizes leptin-driven MDSC expansion. CXCR4/CXCL12 axis disruption impairs MDSC hepatic homing. Anti-αMβ2 antibodies or STAT3 inhibitors block the CCN1/αMβ2/STAT3 signaling cascade, reducing MDSC expansion and immunosuppressive function. All strategies remain preclinical in MAFLD mouse models unless otherwise indicated. Green arrows with ⊕ denote promotion or activation; dark red arrows with ⊖ denote inhibition or blockade. Grey arrows indicate bidirectional or reciprocal interactions. Unidirectional orange arrows indicate cellular state transitions (e.g., HSC activation, transdifferentiation). MAFLD, metabolic dysfunction-associated fatty liver disease; BM, bone marrow; G-MDSCs, granulocytic myeloid-derived suppressor cells; M-MDSCs, monocytic myeloid-derived suppressor cells; Hep, hepatocyte; Mφ, macrophage; DC, dendritic cell; KC, Kupffer cell; NK, natural killer; HSC, hepatic stellate cell; IL, interleukin; TGF-β, transforming growth factor-β; ROS, reactive oxygen species; ARG1, arginase-1; PD-L1, programmed death ligand-1; HIF-1α, hypoxia-inducible factor-1α; STAT3, signal transducer and activator of transcription 3; CCR5i, CCR5 inhibitor; CCN1, cysteine-rich protein 61; ECM, extracellular matrix.

tion of regulatory T cells (Tregs), further dampening effector T-cell activity and reducing immune-mediated clearance of hepatic lipid deposits. TGF-β directly promotes hepatic lipid storage by upregulating key lipogenic enzymes, including fatty acid synthase and acetyl-CoA carboxylase. In a choline-deficient amino acid-defined (CDAA) diet-induced MASH model, hepatocyte-specific deletion of *Tgfr2* (*Tgfr2*^{ΔHEP}) significantly reduced serum alanine aminotransferase (ALT) and triglyceride levels, lowered the MAFLD activity score, and attenuated steatosis, inflammation, and hepatocellular ballooning, indicating that hepatocyte-intrinsic TGF-β signaling promotes liver injury, steatosis, and inflammation in CDAA-fed mice and thereby promotes disease progression. Moreover, TGF-β binds to receptors on T cells and suppresses their proliferation and cytotoxic activity. Second, MDSCs alter the hepatic metabolic state by modulating lipid metabolism-related signaling pathways. Compared with mice fed a normal diet, high-fat diet (HFD)-fed mice show a

significant increase in hepatic MDSC abundance, accompanied by marked activation of the STAT3 signaling pathway and elevated levels of phosphorylated STAT3.²⁴ Conversely, CCR5-deficient G-MDSCs display reduced STAT3 activity in the hepatic microenvironment, which suppresses the expression of lipogenic genes such as acetyl-CoA carboxylase 1 and stearoyl-CoA desaturase 1, thereby reducing de novo lipogenesis.²⁴ In a bone-marrow chimera model with G-MDSC-specific CCR5 deficiency ($n = 6$ per group), hepatic triglyceride content, hepatocyte phospho-STAT3 levels, and Acetyl-CoA carboxylase 1 (*Acc1*)/Stearoyl-CoA desaturase 1 (*Scd1*) mRNA expression were all significantly reduced compared with controls (all $P < 0.05$); conversely, global CCR5 knockout aggravated steatosis, with increased liver weight/body weight ratio, serum aspartate aminotransferase (AST) and alkaline phosphatase (ALP), and hepatic triglycerides (all $P < 0.05$, $n = 6$). These findings suggest that MDSCs influence hepatic lipid accumulation and metabolism, at least

in part, through regulation of STAT3-dependent metabolic programs. Finally, hepatic lipid accumulation itself can promote the expansion and activation of MDSCs. Lipotoxic molecules such as ceramides released in steatotic livers stimulate MDSC proliferation and functional activation. Indeed, MDSC activation has been reported to be closely associated with hepatic fatty acid accumulation, arachidonic acid metabolic dysregulation, and ceramide overload, all of which may contribute to MAFLD progression.^{25,26} Consistent with this, HFD-fed mice exhibit enhanced differentiation of myeloid progenitors into MDSCs together with stronger immunosuppressive activity compared with mice fed a normal diet.²⁷

MDSCs promote persistent hepatic inflammation

MDSCs also play a major immunoregulatory role in hepatic inflammation. They secrete immunosuppressive cytokines,²⁸ including IL-10, TGF- β , and IL-6, which suppress local immune responses and thereby facilitate the persistence of chronic inflammation. As previously discussed, MDSC-derived IL-10 and TGF- β establish an immunosuppressive microenvironment that perpetuates inflammation. In the inflammatory context, these cytokines additionally suppress DC activation and weaken immune-mediated clearance of inflamed hepatic tissue. In parallel, TGF- β , together with MDSC-derived ROS, ARG1, and PGE2, suppresses T-cell activity, while PD-L1/PD-L2-PD-1 interactions further drive T-cell dysfunction.¹⁵ In a polyunsaturated fatty acid diet-induced mouse model, MDSC-derived IL-6 promoted hepatic macrophage activation and proinflammatory mediator release through activation of the JAK-STAT3 pathway, thereby contributing to sustained and chronic hepatic inflammation. IL-6 acts synergistically with ROS and ARG1 produced by MDSCs to establish an immunosuppressive microenvironment that perpetuates chronic liver inflammation. In HFD-induced obese mice, factors associated with MDSCs are markedly altered in hepatic tissue, with significant upregulation of both transcript and protein levels of monocyte chemoattractant protein-1 (MCP-1), S100A8, and S100A9.²⁹ Among these, MCP-1 may mediate the migration of MDSCs from the peripheral circulation into the liver, thereby facilitating the formation of a chronic inflammatory niche. Quantitatively, circulating CD11b+Gr-1+ MDSCs in HFD-fed mice reached $22.20\% \pm 2.99\%$ of leukocytes versus $7.00\% \pm 0.48\%$ in lean controls (an approximately three-fold increase, $P < 0.05$), while hepatic S100A8 and S100A9 transcripts were elevated 2.5- and 2.3-fold (both $P < 0.01$) and their protein levels 3.1- and 1.6-fold (both $P < 0.001$), respectively.

Consistent with these experimental observations, MDSC abundance has been reported to increase in livers affected by chronic liver disease, where these cells accumulate in inflammatory regions and correlate positively with the severity of hepatic inflammation and the stage of fibrosis. In a cohort of 98 patients with chronic liver disease, hepatic CD33+/HLA-DR- MDSC abundance correlated positively with both histological inflammation grade (Spearman $r = 0.610$, $P < 0.001$) and fibrosis stage ($r = 0.687$, $P < 0.001$), and was significantly elevated in hepatitis, cirrhosis, and hepatocellular carcinoma tissues versus normal liver (all $P < 0.001$). Although these findings suggest a potential link in human liver disease, they warrant validation in MAFLD-specific cohorts. In methionine-choline-deficient (MCD) diet-induced mouse models, MDSCs are mainly localized within inflammatory cell clusters and produce abundant ROS, directly participating in the pathological progression of hepatic inflammation.¹⁵ Taken together, these findings indicate that MDSCs regulate immune responses through multiple interconnected mechanisms, establish an immunosuppressive microenviron-

ment, prevent efficient clearance of hepatic inflammation, and may further aggravate liver injury, thereby sustaining and promoting chronic inflammatory progression in MAFLD. Critically, the bidirectional crosstalk between MDSCs and KCs represents a key axis in this process: MDSCs suppress KC self-renewal through TGF- β -dependent mechanisms, while lipotoxic hepatocytes release ceramides that activate MDSCs, creating a self-perpetuating cycle of immune dysregulation.

MDSCs promote the progression of liver fibrosis

During the progression of MAFLD, expansion of MDSCs is closely associated with hepatic fibrogenesis. By exerting potent immunosuppressive effects, MDSCs may weaken hepatic repair mechanisms and thereby accelerate the transition from MAFLD to MASH, cirrhosis, and even hepatocellular carcinoma.³⁰ The profibrotic role of MDSCs is primarily reflected in their ability to promote activation of hepatic stellate cells (HSCs) through the secretion of immunosuppressive and regulatory cytokines, thereby accelerating fibrotic remodeling. In carbon tetrachloride (CCl₄)-induced murine liver injury models, MDSCs recruited to the injured liver exhibit increased expression of multiple cytokines, including IL-10, VEGF, and TGF- β .^{14,23} HSCs are non-parenchymal cells located in the space of Disse and normally remain in a quiescent state; following liver injury, however, they proliferate and become activated. MDSCs can directly induce HSC activation through secretion of TGF- β , driving their transdifferentiation into myofibroblasts, the key effector cells of liver fibrosis that synthesize and secrete collagen. In parallel, IL-10 and TGF- β derived from MDSCs may act synergistically to further enhance HSC activation and collagen production. In both high-fat-high-carbohydrate (HFHC) diet-induced and CCl₄-induced mouse models of liver fibrosis, MDSCs upregulate PPP1R15A through TGF- β signaling, which in turn promotes expression of ARG1 and S100A8/9 while suppressing T-cell proliferation.²³ In addition, MDSCs generate ROS, thereby inducing oxidative stress, whereas S100A8/9 proteins can further promote inflammation and fibrogenesis through ROS-dependent pathways.

Notably, MDSCs may also exert a negative feedback loop after hepatic injury by suppressing excessive inflammation and thereby partially attenuating fibrotic progression.^{31,32} Infusion of bone marrow cells containing MDSCs into patients or mice with liver fibrosis has been shown to inhibit fibrogenesis. In particular, the CD11b+Gr-1+/high F4/80- subpopulation promotes increased IL-10 expression by activated HSCs, reduces hepatic collagen production, and consequently alleviates liver fibrosis. Quantitatively, in CCl₄-induced fibrotic mice (8–12 per group), infusion of CD11b+Gr-1+ bone marrow cells significantly reduced α -SMA and COL1A1 mRNA in isolated HSCs within 24 h (α -SMA: $P < 0.05$; COL1A1: $P < 0.01$), expanded hepatic regulatory T cells, and reduced F4/80+ macrophage infiltration (both $P < 0.05$); these antifibrotic effects were abolished when IL-10-deficient bone marrow cells were used, establishing IL-10 dependence.³³ Similarly, accumulation of monocytic MDSCs (M-MDSCs) in the livers of bile duct-ligated mice can suppress fibrosis progression.³⁴ However, this effect is not uniformly beneficial. The immunosuppressive activity of MDSCs can also reshape the hepatic immune microenvironment, rendering hepatocytes more susceptible to injury and potentially accelerating fibrotic development.¹⁷ Thus, the role of MDSCs in liver fibrosis appears to be highly context-dependent, with both protective and pathogenic consequences. These seemingly contradictory findings reflect the context-dependent functional plasticity of MDSCs, which is systematically analyzed in the following section.

Table 1. Mechanism-centered roles of MDSCs in MAFLD progression

Process	Core Mechanism	Key Molecules	Major Consequence	Quantitative Evidence	Evidence Level*
Hepatic steatosis	Suppression of immune clearance; promotion of lipogenesis	IL-10, TGF- β , STAT3, ACC1, SCD1	Lipid accumulation	G-MDSC-specific CCR5 deficiency (bone-marrow chimera, $n = 6/\text{group}$): hepatic triglycerides, hepatocyte phospho-STAT3, and <i>Acc1/Scd1</i> mRNA all significantly reduced vs controls (all $P < 0.05$) ²⁴ ; conversely, global CCR5-KO on HFD increased liver weight/body weight ratio, serum AST and ALP, and hepatic triglycerides (all $P < 0.05$, $n = 6$) ²⁴	Mouse: 14,23,24; Human: limited
Chronic inflammation	Establishment of immuno-suppressive niche	IL-6, IL-10, TGF- β , ARG1, ROS, PD-L1/PD-1	Persistent inflammation	HFD mice: circulating CD11b+Gr-1+ MDSCs $22.20\% \pm 2.99\%$ vs $7.00\% \pm 0.48\%$ in lean controls ($\sim 3\text{-fold}$, $P < 0.05$); hepatic S100A8/S100A9 mRNA increased 2.5- and 2.3-fold (both $P < 0.01$). ²⁹ Human cohort ($n = 98$): hepatic CD33+/HLA-DR- MDSC density correlated with inflammation grade (Spearman $r = 0.610$, $P < 0.001$) ³²	Mouse: 15,29; Human: 32 (correlation)
Fibro-genesis	Activation of HSCs; promotion of collagen synthesis	TGF- β , IL-10, VEGF, S100A8/9, ROS	ECM deposition, fibrosis	Human cohort ($n = 98$): hepatic MDSC density correlated with fibrosis stage (Spearman $r = 0.687$, $P < 0.001$) and was elevated in hepatitis, cirrhosis and HCC vs normal liver (all $P < 0.001$). ³² Mouse CCl ₄ model ($n = 8\text{--}12/\text{group}$): CD11b+Gr1+ BMC infusion reduced HSC α -SMA and COL1A1 mRNA within 24 h (α -SMA: $P < 0.05$; COL1A1: $P < 0.01$) in an IL-10-dependent manner, supporting the opposing anti-fibrotic arm ³³	Mouse: 14,23,33; Human: 32

*Evidence Level: Mouse = murine model data; Human = clinical evidence; limited = preliminary or correlation-only data. G-MDSC, granulocytic myeloid-derived suppressor cell; M-MDSC, monocytic myeloid-derived suppressor cell; CCR5, C-C chemokine receptor type 5; STAT3, signal transducer and activator of transcription 3; ACC1, acetyl-CoA carboxylase 1; SCD1, stearoyl-CoA desaturase 1; KO, knockout; HFD, high-fat diet; AST, aspartate aminotransferase; ALP, alkaline phosphatase; IL, interleukin; TGF- β , transforming growth factor- β ; ARG1, arginase-1; ROS, reactive oxygen species; PD-L1, programmed death ligand-1; HSC, hepatic stellate cell; α -SMA, alpha-smooth muscle actin; COL1A1, collagen type I alpha 1 chain; BMC, bone-marrow cell; HCC, hepatocellular carcinoma.

Context-dependent dual roles of MDSCs in MAFLD

While the preceding sections emphasize the pathogenic contributions of MDSCs to steatosis, inflammation, and fibrosis, accumulating evidence indicates that their functions are not unidirectionally deleterious. Rather, MDSCs exhibit context-dependent plasticity, with both protective and pathogenic consequences shaped by subset composition, disease stage, and microenvironmental cues (Fig. 1). A critical appraisal of this dualistic nature is essential for designing rational therapeutic strategies that preserve beneficial immune regulation while targeting pathogenic MDSC activity. The multifaceted and context-dependent contributions of MDSCs to MAFLD progression are summarized in Table 1.^{14,15,23,24,29,32,33}

Subset-specific functional plasticity

Granulocytic MDSCs (G-MDSCs) predominantly exert pro-inflammatory and profibrotic effects through ROS and ARG1, whereas monocytic MDSCs (M-MDSCs) may adopt an anti-fibrotic phenotype under certain conditions. In bile duct-ligated mice, hepatic M-MDSC accumulation suppresses fibrosis progression,³⁴ whereas in CCl₄-induced injury, CD11b+Gr-1+/high cells promote IL-10-mediated HSC quiescence.³³ Conversely, G-MDSCs appear consistently associated with STAT3-driven lipogenesis and chronic inflammation.²⁴ This subset dichotomy suggests that therapeutic strategies must distinguish between G-MDSC and M-MDSC modulation to avoid inadvertently abrogating protective immune regulation. Furthermore, the differential reliance on immunosuppressive mechanisms—G-MDSCs primarily utilizing ROS/ARG1 and M-MDSCs employing NO, IL-10, and TGF- β —implies that targeted interventions may yield distinct functional outcomes depending on which subset predominates in a given disease context.

Stage-dependent functional shifts

During the simple steatosis stage of MAFLD, MDSC-mediated

immunosuppression may attenuate lipotoxicity-driven inflammation by limiting effector T-cell responses and promoting regulatory T-cell expansion.¹⁴ However, as disease progresses to metabolic dysfunction-associated steatohepatitis (MASH) and liver cirrhosis, sustained MDSC accumulation fosters an immunosuppressive niche that prevents efficient resolution of inflammation, promotes HSC activation, and potentially facilitates immune evasion during hepatocellular transformation.³⁰ Thus, the net effect of MDSCs transitions from transient tissue protection in early injury to chronic pathogenic remodeling in advanced disease. This stage-dependent paradigm has important therapeutic implications: interventions aimed at MDSC depletion in early-stage MAFLD might inadvertently remove transiently protective immune regulation, whereas in advanced fibrosis, selective suppression of pathogenic G-MDSCs while preserving M-MDSC-mediated repair mechanisms may represent a more nuanced approach.

Microenvironmental determinants

The functional polarity of MDSCs is further dictated by local microenvironmental cues. Hypoxia-inducible factor-1 α (HIF-1 α) stabilization in steatotic livers promotes MDSC recruitment and enhances their suppressive capacity through upregulation of glycolytic metabolism and PD-L1 expression. TGF- β concentration gradients appear critical: low-level TGF- β sustains MDSC suppressive programming through SMAD-dependent transcriptional activation, whereas high concentrations in fibrotic foci drive myofibroblast differentiation and collagen deposition via non-canonical pathways.²³ Additionally, ceramide-enriched lipotoxic environments stimulate MDSC expansion but may alter their cytokine profile toward enhanced IL-6 and reduced IL-10 production,^{25,26} tipping the balance toward pathogenicity. Understanding these contextual switches is essential for designing stage-selective MDSC interventions. Notably, the reciprocal interactions be-

tween MDSCs and hepatocytes—wherein lipotoxic hepatocytes activate MDSCs through ceramide release, and MDSCs in turn suppress hepatocyte-autonomous immune surveillance—exemplify the complex feedback loops that govern MDSC function in the MAFLD microenvironment.

Critical appraisal: The concept of MDSC plasticity in MAFLD is predominantly derived from murine models utilizing dietary (MCD, HFD) or toxic (CCl_4) injury paradigms. Whether the protective functions observed in these experimental systems translate to human MAFLD remains uncertain. No prospective human studies have directly assessed MDSC subset switching across MAFLD stages, and the limited clinical data (e.g., Ref 32) remain correlative rather than mechanistic. Human MDSCs are phenotypically defined by CD14[−]/low-CD15⁺ or HLA-DR[−]-CD33⁺ markers rather than the murine CD11b⁺-Gr-1⁺ system, and cross-species functional conservation has not been rigorously validated. Future studies employing humanized models and prospective clinical cohorts are urgently needed to define the therapeutic window within which MDSC modulation might be beneficial versus harmful.

Quantitative interpretation of evidence presented in Table 1. The murine lipogenesis data (G-MDSC-specific CCR5 deficiency, $n = 6$ per group) demonstrate effect sizes consistent with biological relevance—hepatic triglyceride reduction, attenuated phospho-STAT3, and downregulation of *Acc1/Scd1* mRNA (all $P < 0.05$)—yet the small sample size and absence of confidence intervals preclude robust effect-size estimation. The human correlation data ($n = 98$) yield r values of 0.610–0.687, reflecting moderate-to-strong monotonic associations between hepatic MDSC density and histological severity. These coefficients should not be interpreted as the proportion of outcome variance explained in a regression framework, as they derive from nonparametric Spearman correlation. Clinically, an $r = 0.687$ for fibrosis stage suggests that MDSC density cannot reliably discriminate individual patients across fibrosis stages without substantial overlap, reinforcing the need for multiparameter models rather than single-cell metrics.

Evidence-level and clinical-stage assessment of therapeutic strategies are shown in Table 2.^{24,29,35–38} All five strategies remain at the preclinical or early translational phase in MAFLD. MitoTEMPO and anti- $\alpha\text{M}\beta 2/\text{STAT3}$ inhibition are supported by quantitative mechanistic evidence, yet neither has entered human MAFLD trials. CCR5 antagonism (maraviroc) has the most advanced clinical footprint, but the Hepmarc and MAVMET trials were feasibility/phase II studies in HIV-coinfected populations with negative efficacy signals for hepatic endpoints; this evidence level is insufficient to support off-label use in immunocompetent MAFLD. Leptin-receptor blockade and CXCR4/CXCL12 disruption have promising murine efficacy data but lack dose-response characterization, pharmacokinetic profiling, and toxicity assessment. Collectively, no MDSC-targeted strategy currently meets the threshold for clinical recommendation; the certainty of evidence for all strategies is low to very low per GRADE criteria. All should be regarded as experimental interventions warranting controlled phase I/II mechanistic trials in MAFLD-specific populations.

Targeted therapeutic strategies

Current preclinical and emerging clinical strategies directed at MDSCs or their upstream signaling pathways are outlined in Table 2. At present, MDSC-directed therapies in MAFLD remain largely preclinical. However, several targets have progressed toward clinical evaluation in related metabolic diseases. Notably, CCR5 antagonists, originally developed for

HIV therapy, have entered early-phase trials for metabolic dysfunction-associated steatohepatitis (MASH), although their specific effects on MDSC reprogramming in human liver remain uncharacterized. The following sections summarize preclinical findings and explicitly note translational gaps that must be addressed prior to clinical deployment.

Mitochondrial antioxidant MitoTEMPO

Studies based on high-fat diet (HFD)-induced MAFLD mouse models have shown that the mitochondrial antioxidant MitoTEMPO significantly attenuates hepatic steatosis and inflammatory responses.²⁹ Following MitoTEMPO treatment, the number of MDSCs in both the liver and peripheral blood was markedly reduced, accompanied by a clear decrease in the degree of hepatic steatosis. In addition, MitoTEMPO suppressed the expression of MDSC-associated proinflammatory mediators, including MCP-1, S100A8, and S100A9. Quantitatively ($n = 5$ –8 mice per group), MitoTEMPO reduced hepatic S100A8 and S100A9 mRNA by 5.9- and 5.2-fold ($P < 0.001$), their protein levels by 1.9- and 1.4-fold ($P < 0.01$), and MCP-1 mRNA and protein ($P < 0.001$); notably, the reduction in circulating MDSC frequency (from 22.20% $\pm$ 2.99% to 12.52% $\pm$ 1.22%) reached statistical significance ($P < 0.05$), indicating that MitoTEMPO reduced circulating MDSC frequency and its associated proinflammatory mediators. **Clinical Translation Challenges:** No clinical trials have evaluated MitoTEMPO in MAFLD to date. Its systemic antioxidant effects may disrupt physiological ROS signaling required for normal immune responses, warranting careful dose-escalation studies. Furthermore, the pharmacokinetics of mitochondria-targeted antioxidants in human liver tissue remain poorly characterized, and off-target effects on non-MDSC immune populations have not been assessed.

Targeting the chemokine receptor CCR5

Evidence indicates that the chemokine receptor CCR5 plays an important role in the pathological progression of MAFLD.²⁴ This receptor is expressed not only in hepatocytes but also in G-MDSCs. In the MAFLD microenvironment, CCR5 signaling sustains the immunosuppressive secretory program of G-MDSCs (IL-10, TGF- β , and PD-L1); blockade of CCR5 in G-MDSCs attenuates this program while markedly reducing STAT3 phosphorylation, lipogenic gene expression, and proinflammatory mediator production in adjacent hepatocytes, thereby decreasing hepatic lipid deposition and inflammatory infiltration in mice. In the supporting bone-marrow chimera study ($n = 6$ per group), G-MDSC-specific CCR5 deficiency significantly reduced hepatic triglyceride content, hepatocyte phospho-STAT3 levels, and *Acc1/Scd1* mRNA expression versus controls (all $P < 0.05$). However, clinical translation remains unproven: in the 96-week Hepmarc randomized feasibility trial ($n = 53$; 23 receiving add-on maraviroc) in people with HIV and MAFLD, adherence reached 92% and no serious adverse reactions occurred, yet there were no significant between-group differences in liver stiffness, controlled attenuation parameter, or enhanced liver fibrosis score changes, with 95% confidence intervals for ALT and liver stiffness trends containing zero; consistently, the 48-week MAVMET randomized trial ($n = 90$) found no MRI-PDFF liver-fat reduction with maraviroc versus control.³⁵ These observations suggest that CCR5 inhibition may represent a promising therapeutic strategy for MAFLD, although efficacy in immunocompetent MAFLD patients has yet to be demonstrated.

Repurposing Potential and Species-Specific Barriers: While CCR5 inhibition reduces G-MDSC-mediated STAT3 activation in murine models, human G-MDSCs are defined by CD15⁺-CD33⁺ rather than Ly6G⁺ markers, and wheth-

Table 2. MDSC-targeted therapeutic strategies in MAFLD

Target/Strategy	Mechanism	Effect on MDSCs	Quantitative Evidence	Evidence Level	Clinical Stage
Mito-TEMPO	Mitochondrial ROS scavenging	Down MDSC expansion, down proinflammatory mediators	HFD mice ($n = 5-8/\text{group}$): hepatic S100A8 and S100A9 mRNA reduced 5.9- and 5.2-fold ($P < 0.001$), protein 1.9- and 1.4-fold ($P < 0.01$), and MCP-1 reduced ($P < 0.001$). ²⁹ Circulating MDSC frequency fell from $22.20\% \pm 2.99\%$ to $12.52\% \pm 1.22\%$, and the decrease was significant ($P < 0.05$), indicating reduced circulating MDSC frequency ²⁹	Mouse (HFD model)	Preclinical
CCR5 inhibition	Blockade of CCR5 signaling	Down G-MDSC anti-inflammatory program, down STAT3	Mouse, G-MDSC-specific CCR5 deficiency (chimera, $n = 6/\text{group}$): hepatic triglycerides, hepatocyte phospho-STAT3, and <i>Acc1/Scd1</i> mRNA all reduced ($P < 0.05$). ²⁴ Human: the 96-week Hepmarc feasibility trial ($n = 53$; add-on maraviroc $n = 23$, HIV+MAFLD) found no significant between-group differences in LSM, CAP, or ELF change, with 95% CIs containing zero ³⁵ ; the 48-week MAVMET RCT ($n = 90$) likewise found no MRI-PDFF liver-fat reduction with maraviroc	Mouse ²⁴ ; Human (feasibility RCT) ³⁵	Emerging clinical interest*
Leptin receptor blockade	Antagonism of leptin signaling	Down MDSC abundance	HFD-fed mice: soluble leptin receptor (leptin antagonist) significantly reduced MDSC abundance vs controls ($P < 0.05$; 3 treated mice and 14 controls pooled from two experiments); conversely, anti-Gr-1-mediated MDSC depletion aggravated insulin resistance and adipose inflammation. ^{36,37} Effect size not reported in primary source (absolute counts and percentage change unavailable)	Mouse	Preclinical
CXCR4/CXCL12 axis	Disruption of hepatic recruitment	Down MDSC liver infiltration	Mouse MASH model: adoptive transfer of exogenous MDSCs significantly reduced serum ALT and AST vs controls ($P < 0.05$) ⁴⁰ ; absolute values and effect size not reported in primary source. Quantitative reduction of MDSC infiltration after pharmacological CXCR4 blockade in MAFLD has not been reported; in a chronic CCl ₄ model the CXCR4 antagonist AMD3100 aggravated fibrosis with increased intrahepatic neutrophils, underscoring context-dependence	Mouse	Preclinical
Anti-alphaM-beta2 / STAT3i	Blockade of CCN1/alphaM-beta2/STAT3 axis	Down MDSC expansion & function	In vitro human system ($n = 6$): the STAT3 inhibitor Stattic completely abrogated CCN1+GM-CSF-induced MDSC expansion, and $\alpha\text{M}\beta_2$ -neutralizing antibody significantly reduced expansion (Stattic: $P < 0.01$; $\alpha\text{M}\beta_2$ antibody: $P < 0.05$); CCN1-expanded MDSCs suppressed T-cell proliferation via iNOS, reversed by the iNOS inhibitor 1400W ($P < 0.05$) ³⁸	Human <i>in vitro</i> ³⁸	Preclinical

*CCR5 inhibitors (e.g., maraviroc) have shown emerging interest in metabolic liver diseases. In the 96-week Hepmarc feasibility trial ($n = 53$) and the 48-week MAVMET RCT ($n = 90$) in people with HIV and MAFLD, maraviroc demonstrated acceptable safety but no significant efficacy on elastography, CAP, ELF, or MRI-PDFF endpoints, and MDSC reprogramming was not assessed; no trials in immunocompetent MAFLD populations have been completed as of this writing. ROS, reactive oxygen species; MDSC, myeloid-derived suppressor cell; S100A8/A9, S100 calcium-binding protein A8/A9; MCP-1, monocyte chemoattractant protein-1; HFD, high-fat diet; CCR5, C-C chemokine receptor type 5; G-MDSC, granulocytic myeloid-derived suppressor cell; STAT3, signal transducer and activator of transcription 3; MRI-PDFF, magnetic resonance imaging proton density fat fraction; HIV, human immunodeficiency virus; NAFLD, nonalcoholic fatty liver disease; RCT, randomized controlled trial; CXCR4, C-X-C chemokine receptor type 4; CXCL12, C-X-C motif chemokine ligand 12; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCl₄, carbon tetrachloride; CCN1, cellular communication network factor 1; $\alpha\text{M}\beta_2$, alpha-M beta-2 integrin; GM-CSF, granulocyte-macrophage colony-stimulating factor; iNOS, inducible nitric oxide synthase.

er CCR5 blockade produces equivalent phenotypic effects in human MAFLD requires validation. The optimal timing of CCR5-targeted intervention during disease progression also remains undefined. Notably, CCR5 antagonists such as maraviroc have entered early-phase trials for MASH,³⁶ although their specific effects on MDSC reprogramming in human liver remain uncharacterized.

Blockade of the leptin receptor

Obesity-related metabolic inflammation promotes the expansion and activation of MDSCs by upregulating proinflammatory mediators such as IL-6, TNF- α , and PGE2.³⁶ Under obese conditions, MDSCs infiltrate the peripheral circulation, liver, and adipose tissue.^{37,40} Leptin, an adipose-derived hormone, plays a central role in regulating energy balance, appetite, and multiple metabolic processes. One study³⁷ demonstrated that leptin promotes MDSC accumulation, whereas MDSCs in turn suppress leptin levels through a negative-feedback

mechanism. Animal experiments further demonstrated that administration of a soluble leptin receptor, which antagonizes leptin signaling, significantly reduces MDSC abundance in HFD-fed mice ($P < 0.05$ versus controls); however, the primary study did not report absolute MDSC counts, percentage changes, or per-group sample sizes, precluding effect-size estimation. This incomplete quantitative reporting is explicitly acknowledged as an evidence gap in the Critical Appraisal section. Conversely, depletion of MDSCs by anti-Gr-1 antibodies aggravates insulin resistance and adipose tissue inflammation, indicating that MDSCs play a critical role in obesity-associated metabolic dysregulation.⁴⁰ Detailed quantitative effect sizes for leptin-receptor blockade in MAFLD await reporting in future studies; the available evidence confirms statistical significance ($P < 0.05$) without enabling precise magnitude estimation.³⁶

Systemic Safety Constraints and Metabolic Interconnectivity: Leptin resistance in advanced obesity complicates solu-

ble receptor strategies; clinical translation must account for the disconnect between circulating leptin levels and central leptin sensitivity. Moreover, systemic leptin antagonism may disrupt neuroendocrine regulation of energy homeostasis, raising safety concerns that have limited clinical development. Human MDSC responses to leptin blockade have not been evaluated.

Targeting the CXCR4/CXCL12 axis

Studies have demonstrated that administration of exogenous MDSCs significantly lowers serum ALT and AST levels in mouse models of MASH ($P < 0.05$ versus controls), suggesting a potential effect on biochemical markers of hepatic injury⁴¹; however, absolute enzyme values, per-group sample sizes, and effect sizes were not reported in the primary study, precluding quantitative synthesis. The signaling axis formed by CXCR4 and its ligand CXCL12 is a key pathway mediating hepatic recruitment of MDSCs. In the MASH microenvironment, CXCL12 expression is upregulated, attracting MDSCs into the liver and thereby aggravating inflammation and fibrosis. This axis also participates in remodeling of the hepatic immune microenvironment by regulating both the quantity of recruited MDSCs and their immunosuppressive activity. These findings suggest that therapeutic intervention targeting the CXCR4/CXCL12 axis may offer a new direction for MASH treatment. However, quantitative reductions in MDSC hepatic infiltration following pharmacological CXCR4 blockade have not been reported in MAFLD models, and in a chronic CCl₄ model the CXCR4 antagonist AMD3100 paradoxically aggravated fibrosis with increased intrahepatic neutrophil accumulation, underscoring the context-dependence of this axis.

Chronic Dosing Paradox and Hematopoietic Trade-offs: CXCR4 antagonists (e.g., plerixafor) are approved for stem cell mobilization but have not been evaluated in MAFLD. Given the essential role of CXCR4 in hematopoietic stem cell homing, long-term blockade may impair bone marrow function, necessitating intermittent rather than continuous dosing strategies. Whether CXCR4/CXCL12 disruption selectively reduces pathogenic MDSC recruitment without compromising protective immune cell trafficking remains unknown.

Anti- $\alpha\text{M}\beta_2$ antibodies or STAT3 inhibitors

Recent studies have identified cysteine-rich protein 61 (Cyr61/CCN1) as a liver injury-associated molecule that is highly expressed in a liver-specific manner during MAFLD progression and positively correlates with the degree of hepatic MDSC infiltration.³⁸ CCN1 binds to the integrin $\alpha\text{M}\beta_2$ receptor on the surface of MDSCs, activates a STAT3 phosphorylation cascade, and thereby drives both MDSC expansion and enhancement of their immunosuppressive function. Experimental evidence indicates that blockade of integrin $\alpha\text{M}\beta_2$ or pharmacological inhibition of the STAT3 pathway can significantly reverse the CCN1-mediated expansion of MDSCs: in an *in vitro* human system ($n = 6$), the STAT3 inhibitor Stattic completely abrogated CCN1+GM-CSF-induced MDSC expansion and $\alpha\text{M}\beta_2$ -neutralizing antibody significantly reduced expansion (Stattic: $P < 0.01$; $\alpha\text{M}\beta_2$ antibody: $P < 0.05$), while CCN1-expanded MDSCs suppressed T-cell proliferation via iNOS, an effect reversed by the iNOS inhibitor 1400W ($P < 0.05$). Notably, this evidence derives from human *in vitro* experiments rather than murine models, strengthening its translational relevance. These findings confirm that the CCN1/ $\alpha\text{M}\beta_2$ /STAT3 signaling axis represents a critical molecular pathway underlying immune microenvironmental dysregulation in MAFLD (Fig. 1).

Druggability Hurdles and Cell-Specific Delivery Imperatives: STAT3 inhibitors face significant safety hurdles given the pleiotropic roles of STAT3 in normal physiology, including liver regeneration and immune surveillance. The therapeutic window for MDSC-specific STAT3 inhibition may be narrow, requiring targeted delivery systems to minimize off-target effects.

Emerging potential of MDSCs as noninvasive biomarkers

Beyond therapeutic targeting, circulating MDSCs and their secreted mediators (e.g., S100A8/A9, arginase activity) may serve as noninvasive biomarkers for MAFLD staging.⁴² In patients with chronic liver disease, hepatic MDSC abundance correlates with inflammation grade and fibrosis stage (in a cohort of 98 patients, Spearman $r = 0.610$ and $r = 0.687$, respectively; both $P < 0.001$).³² However, standardized immunophenotyping protocols for human MDSCs remain inconsistent, ranging from CD14+/CD15+ gating to Lin-HLA-DR-CD33+ definitions, limiting cross-study comparability. Future research should integrate single-cell transcriptomics and spatial profiling to define subset-specific signatures that complement existing noninvasive scores such as NFS and FIB-4.^{43,44} The development of MDSC-derived exosomal cargo assays may further enable liquid biopsy approaches for monitoring disease progression and treatment response in MAFLD patients.

Clinical-grade quantitative appraisal of MDSC biomarker potential. The correlation coefficients reported in the human cohort ($r = 0.610$ – 0.687) reflect moderate-to-strong monotonic associations; however, their clinical interpretability is constrained by several statistical and methodological factors. First, the sample size ($n = 98$) provides adequate power (>0.99) to detect correlations of this magnitude at $\alpha = 0.05$, yet subgroup stratification by MAFLD etiology, BMI, or glycemic status was not performed, precluding assessment of effect modification. Second, the cohort was predominantly HBV-related, introducing substantial spectrum bias that limits generalizability to metabolically defined MAFLD. Third, immunohistochemical CD33+/HLA-DR- phenotyping lacks the precision of multiparameter flow cytometry and was not validated against interobserver agreement metrics (e.g., κ statistic). Fourth, no multivariable models adjusting for age, sex, insulin resistance, or concomitant therapies were reported, leaving residual confounding unquantified. Fifth, and most critically, receiver-operating characteristic (ROC) analysis, optimal cutoff determination, sensitivity/specificity profiles, and likelihood ratios were absent, meaning the diagnostic and prognostic discrimination of hepatic MDSC density remains uncharacterized. From a clinical decision-making perspective, these data provide proof-of-concept support only: they justify prospective biomarker-development studies but do not yet warrant incorporation into MAFLD screening algorithms, biopsy-avoidance strategies, or treatment-response monitoring.

Critical appraisal and limitations

In this section, we critically appraise the strengths and limitations of the current MDSC-MAFLD evidence base, explicitly discuss how these methodological constraints limit the clinical applicability of existing findings, and delineate actionable implications for MAFLD screening, staging, and therapeutic development.

Strengths and limitations of animal models. Murine studies offer decisive experimental strengths: (i) genetically homogeneous backgrounds and controlled dietary inter-

ventions (MCD, HFD, HFHC) enable mechanistic isolation of MDSC-driven pathways; (ii) loss-of-function validation via CCR5-deficient bone-marrow chimeras, anti-Gr-1 depletion, and hepatocyte-specific *Tgfb β 2* knockout supports causal inference that cannot be obtained from human observational data; (iii) access to liver tissue permits spatial and single-cell profiling of MDSC-hepatocyte-stellate cell crosstalk. However, these advantages are offset by critical translational limitations. Murine MDSCs are defined by CD11b+Gr-1+ (Ly6G/Ly6C) markers, whereas human equivalents are identified by CD14-/lowCD15+ or HLA-DR-CD33+ phenotypes; cross-species functional conservation has not been rigorously validated. Dietary induction spans weeks to months, whereas human MAFLD develops over decades with superimposed metabolic syndrome, aging, and polypharmacy. Moreover, murine Kupffer cells constitute ~20–30% of hepatic leukocytes versus ~50% in humans, and the gut-liver axis differs markedly in microbial composition and bile-acid metabolism, potentially altering MDSC recruitment kinetics and microenvironmental programming. Consequently, murine data excel at hypothesis generation and preclinical target prioritization but cannot reliably predict human pharmacokinetics, dosing windows, or adverse-event profiles.

Strengths and limitations of human studies. Human evidence provides indispensable ecological validity and direct relevance to clinical phenotypes. The $n = 98$ cohort³² established that hepatic MDSC density increases across the spectrum of chronic liver disease and correlates with histological severity, offering a biologically plausible rationale for biomarker development. Nevertheless, the limitations are equally consequential. The study was cross-sectional, precluding any inference about temporal precedence or disease trajectory. The cohort was predominantly HBV-related rather than MAFLD-specific, meaning the observed MDSC associations may reflect viral rather than metabolic immunopathology. No multivariable adjustment for age, BMI, diabetes, dyslipidemia, or pharmacotherapy was reported, leaving unmeasured confounding unresolved. Immunohistochemistry-based phenotyping (CD33+/HLA-DR-) lacks standardization against flow-cytometric reference methods, and no interobserver reliability data were provided. Finally, no ROC analysis, diagnostic cutoffs, or calibration metrics were generated, meaning the discriminative performance of MDSC density for MAFLD staging versus noninvasive scores (NFS, FIB-4) remains unknown. These constraints relegate the human data to hypothesis-generating status; they do not currently support clinical deployment as diagnostic, prognostic, or predictive biomarkers.

Study-level appraisal shaping clinical inference. The antifibrotic benefit of CD11b+Gr1+ bone-marrow cells was demonstrated in a CCl₄ model (8–12 mice per group) with IL-10 dependence formally established,³³ but acute toxin-induced fibrosis differs fundamentally from chronic metabolic fibrosis in its inflammatory kinetics, collagen cross-linking, and reversibility, severely limiting extrapolation to MAFLD. For MitoTEMPO, the highly significant suppression of S100A8/S100A9 ($P < 0.001$) was accompanied by a significant reduction in MDSC frequency ($P < 0.05$), indicating effects on both MDSC abundance and associated inflammatory mediators.²⁹ Most importantly for clinical practice, the only randomized controlled evidence for an MDSC-relevant target—the Hepmarc ($n = 53$) and MAVMET ($n = 90$) trials of the CCR5 antagonist maraviroc—was conducted in HIV-coinfected, virologically suppressed populations, was not powered for efficacy, and did not measure MDSC reprogramming; their negative hepatic-endpoint results therefore cannot be extrapolated to immunocompetent MAFLD patients, and CCR5 blockade

should presently be regarded as mechanistically promising but clinically unproven.³⁵ The murine evidence for G-MDSC-specific CCR5 targeting rests on a single bone-marrow chimera experiment with only six mice per group, without reported randomization or blinded outcome assessment, and the divergent phenotype of global CCR5 knockout (exacerbated steatosis and liver injury) further cautions against compartment-agnostic clinical extrapolation.²⁴ Finally, the evidence for leptin-receptor blockade and CXCR4/CXCL12-axis intervention is weakened by incomplete quantitative reporting in the primary studies, which precludes cross-strategy comparison and materially lowers confidence in these two targets.^{36,41}

Implications for clinical practice and trial design. The current evidence base generates five actionable, albeit provisional, implications for clinicians and translational researchers:

- Screening and case-finding: Circulating MDSCs should not be adopted as standalone noninvasive screening biomarkers for MAFLD. Until standardized multiparameter flow-cytometric protocols (e.g., Lin-HLA-DR-CD33+ or CD14-/lowCD15+ gating with viability dyes) are validated in prospective, metabolically homogeneous cohorts with appropriately large sample sizes (sufficient for biomarker derivation and external validation), their use in clinical practice is premature.
- Disease staging and biopsy decision-making: Hepatic MDSC density (assessed by immunohistochemistry or in situ hybridization) shows moderate-to-strong correlation with inflammation and fibrosis severity, yet it requires invasive tissue sampling. Its additive value to existing noninvasive scores (NFS, FIB-4, ELF, or vibration-controlled transient elastography) has not been tested. Clinicians should continue to rely on established staging algorithms; MDSC-based assessment remains investigational.
- Noninvasive surrogate development: Serum S100A8/A9 heterodimers and plasma arginase activity represent promising circulating surrogates for hepatic MDSC burden, but normative ranges, intra-individual biological variation, and confounding by systemic inflammation (e.g., infection, autoimmune flare) remain undefined. These analytes should be incorporated into prospective biomarker panels rather than deployed as single-analyte tests.
- Therapeutic target prioritization: MDSC-directed strategies (mitochondrial antioxidants, CCR5 antagonists, leptin-receptor blockade, CXCR4/CXCL12 disruption, STAT3 inhibitors) remain exclusively preclinical in MAFLD. Given the dual protective and pathogenic roles of MDSCs, depletion strategies carry theoretical risks of uncontrolled infection, impaired immune surveillance, and loss of tissue-repair function, particularly in cirrhosis. Any first-in-human trial must include rigorous safety monitoring for infectious complications and hepatic decompensation.
- Clinical trial endpoint design: Future interventional trials should prioritize functional MDSC endpoints (arginase activity, ROS generation, T-cell suppression assays) over simple enumeration, given the dissociation between MDSC frequency and suppressive function observed with MitoTEMPO. Moreover, subset-specific endpoints (G-MDSC vs. M-MDSC) should be prespecified, as these populations exert divergent effects on lipogenesis and fibrogenesis.

Future studies must prioritize: (i) humanized liver-on-chip or organoid models that recapitulate human metabolic comorbidities; (ii) prospective MAFLD-specific cohorts with serial biosampling, standardized immunophenotyping, and multivariable statistical modeling; (iii) randomized mecha-

nistic trials that incorporate MDSC functional endpoints alongside conventional histological and elastographic outcomes; and (iv) rigorous safety profiling of MDSC modulation in cirrhotic and immunocompromised populations to advance MDSC biology from bench to bedside.

Conclusions

MDSCs are increasingly recognized as central immune regulators in the pathogenesis of MAFLD, linking metabolic dysfunction, chronic inflammation, and fibrotic remodeling into an integrated disease network. Rather than acting as bystanders, these cells actively shape the hepatic microenvironment through immunosuppressive cytokines, metabolic mediators, and redox-dependent mechanisms. By modulating macrophage polarization, T-cell activity, dendritic-cell function, hepatic stellate-cell activation, and lipid metabolic signaling, MDSCs participate in multiple stages of disease progression, from steatosis and inflammatory persistence to fibrogenesis and, potentially, transition toward advanced liver injury. Importantly, the available evidence suggests that the effects of MDSCs are not unidirectional; under certain conditions, they may attenuate excessive inflammation and transiently limit tissue damage, whereas in other contexts they promote immune evasion, chronic injury, and fibrosis. This functional plasticity highlights the complexity of MDSC biology in MAFLD and indicates that their pathological significance is highly dependent on subset composition, disease stage, and local microenvironmental cues.

From a translational perspective, MDSCs provide a potential framework for mechanism-based intervention in MAFLD. Experimental studies suggest that mitochondrial antioxidants, chemokine receptor targeting, blockade of leptin signaling, modulation of the CXCR4/CXCL12 axis, and inhibition of the CCN1/ α M β 2/STAT3 pathway may influence MDSC abundance or function and, in preclinical models, modify disease severity. However, current evidence remains largely preclinical, and several critical issues remain unresolved, including the precise distinction between protective and pathogenic MDSC subsets, the reproducibility of animal-model findings in humans, and the risk that excessive suppression of MDSCs may disrupt immune homeostasis. Future research should therefore integrate immunophenotyping, single-cell and spatial approaches, and clinically relevant validation to define MDSC subset-specific functions with greater precision. Such efforts may, in theory, enable the development of selective therapeutic strategies that not only suppress pathogenic inflammation and fibrosis but also preserve essential immune balance, provided that the molecular distinctions between protective and pathogenic MDSC subsets can be reliably defined and pharmacologically targeted. Ultimately, this would advance precision treatment for MAFLD.

Funding

This work was supported by the Kuanren Talents Program of the Second Affiliated Hospital of Chongqing Medical University (No. 2021240308), the General Program of Chongqing Natural Science Foundation (CSTB2022NSCQ-MSX0909), and the Group Medical Aid Project for Tibet Autonomous Region supported by the Natural Science Foundation of Tibet Autonomous Region (XZ2023ZR-ZY75 (Z)).

Conflict of interest

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

Author contributions

Study concept and design: GM, JX, LC; literature search and data extraction: GM, MT, YM; drafting of the manuscript: Guozirui Mou; critical revision of the manuscript for important intellectual content: HZ; administrative, technical, or material support: TZ, XL; study supervision: HZ. All authors have made a significant contribution to this study and have approved the final manuscript.

References

- [1] Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, *et al*. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol* 2020;73(1):202–209. doi:10.1016/j.jhep.2020.03.039, PMID:32278004.
- [2] Younossi ZM, Zelber-Sagi S, Lazarus JV, Wong VW, Yilmaz Y, Duseja A, *et al*. Global Consensus Recommendations for Metabolic Dysfunction-Associated Steatotic Liver Disease and Steatohepatitis. *Gastroenterology* 2025;169(5):1017–1032.e1012. doi:10.1053/j.gastro.2025.02.044, PMID:40222485.
- [3] Younossi ZM, Paik JM, Stepanova M, Ong J, Alqahtani S, Henry L. Clinical profiles and mortality rates are similar for metabolic dysfunction-associated steatotic liver disease and non-alcoholic fatty liver disease. *J Hepatol* 2024;80(5):694–701. doi:10.1016/j.jhep.2024.01.014, PMID:38286339.
- [4] Wu Y, Yi M, Niu M, Mei Q, Wu K. Myeloid-derived suppressor cells: an emerging target for anticancer immunotherapy. *Mol Cancer* 2022;21(1):184. doi:10.1186/s12943-022-01657-y, PMID:36163047.
- [5] Feng G, Valenti L, Wong VW, Fouad YM, Yilmaz Y, Kim W, *et al*. Recompensation in cirrhosis: unravelling the evolving natural history of nonalcoholic fatty liver disease. *Nat Rev Gastroenterol Hepatol* 2024;21(1):46–56. doi:10.1038/s41575-023-00846-4, PMID:37798441.
- [6] [Guidelines for the prevention and treatment of metabolic dysfunction-associated (non-alcoholic) fatty liver disease (Version 2024)]. Zhonghua Gan Zang Bing Za Zhi 2024;32(5):418–434. doi:10.3760/cma.j.cn501113-20240327-00163, PMID:38858192.
- [7] Tilg H, Adolph TE, Moschen AR. Multiple Parallel Hits Hypothesis in Non-alcoholic Fatty Liver Disease: Revisited After a Decade. *Hepatology* 2021;73(2):833–842. doi:10.1002/hep.31518, PMID:32780879.
- [8] Huby T, Gautier EL. Immune cell-mediated features of non-alcoholic steatohepatitis. *Nat Rev Immunol* 2022;22(7):429–443. doi:10.1038/s41577-021-00639-3, PMID:34741169.
- [9] Hammerich L, Tacke F. Hepatic inflammatory responses in liver fibrosis. *Nat Rev Gastroenterol Hepatol* 2023;20(10):633–646. doi:10.1038/s41575-023-00807-x, PMID:37400694.
- [10] Breuer DA, Pacheco MC, Washington MK, Montgomery SA, Hasty AH, Kennedy AJ. CD8(+) T cells regulate liver injury in obesity-related nonalcoholic fatty liver disease. *Am J Physiol Gastrointest Liver Physiol* 2020;318(2):G211–G224. doi:10.1152/ajpgi.00040.2019, PMID:31709830.
- [11] Peiseler M, Schwabe R, Hampe J, Kubes P, Heikenwälder M, Tacke F. Immune mechanisms linking metabolic injury to inflammation and fibrosis in fatty liver disease – novel insights into cellular communication circuits. *J Hepatol* 2022;77(4):1136–1160. doi:10.1016/j.jhep.2022.06.012, PMID:35750137.
- [12] Nati M, Chung KJ, Chavakis T. The Role of Innate Immune Cells in Non-alcoholic Fatty Liver Disease. *J Innate Immun* 2022;14(1):31–41. doi:10.1159/000518407, PMID:34515137.
- [13] Deczkowska A, David E, Ramadori P, Pfister D, Safran M, Li B, *et al*. XCR1(+) type 1 conventional dendritic cells drive liver pathology in non-alcoholic steatohepatitis. *Nat Med* 2021;27(6):1043–1054. doi:10.1038/s41591-021-01344-3, PMID:34017133.
- [14] Zhang Q, Yu T, Tan H, Shi H. Hepatic recruitment of myeloid-derived suppressor cells upon liver injury promotes both liver regeneration and fibrosis. *BMC Gastroenterol* 2024;24(1):163. doi:10.1186/s12876-024-03245-4, PMID:38745150.
- [15] Yan J, Guo S, He J, Huang H, Xu Y. Myeloid-derived suppressor cells in metabolic and cardiovascular disorders. *Trends Endocrinol Metab* 2025;36(11):1043–1053. doi:10.1016/j.tem.2025.02.001, PMID:40024876.
- [16] Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. *Nat Rev Immunol* 2021;21(8):485–498. doi:10.1038/s41577-020-00490-y, PMID:33526920.
- [17] Hegde S, Leader AM, Merad M. MDSC: Markers, development, states, and unaddressed complexity. *Immunity* 2021;54(5):875–884. doi:10.1016/j.immuni.2021.04.004, PMID:33979585.
- [18] Li K, Shi H, Zhang B, Ou X, Ma Q, Chen Y, *et al*. Myeloid-derived suppressor cells as immunosuppressive regulators and therapeutic targets in cancer. *Signal Transduct Target Ther* 2021;6(1):362. doi:10.1038/s41392-021-00670-9, PMID:34620838.
- [19] Sun Q, Dai H, Wang S, Chen Y, Shi H. Progress in research on the role played by myeloid-derived suppressor cells in liver diseases. *Scand J Immunol* 2023;98(4):e13312. doi:10.1111/sji.13312, PMID:38441348.
- [20] Cheung EC, Vousden KH. The role of ROS in tumour development and progression. *Nat Rev Cancer* 2022;22(5):280–297. doi:10.1038/s41568-021-00435-0, PMID:35102280.
- [21] Hoechst B, Voigtlaender T, Ormandy L, Gamrekelashvili J, Zhao F, Wedemeyer H, *et al*. Myeloid derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the Nkp30 receptor. *Hepatology*

- 2009;50(3):799–807. doi:10.1002/hep.23054, PMID:19551844.
- [22] Ugolini A, Tyurin VA, Tyurina YY, Tcyganov EN, Donthireddy L, Kagan VE, *et al*. Polymorphonuclear myeloid-derived suppressor cells limit antigen cross-presentation by dendritic cells in cancer. *JCI Insight* 2020;5(15):e138581. doi:10.1172/jci.insight.138581, PMID:32584791.
- [23] Liu X, Liu M, Wu H, Tang W, Yang W, Chan TTH, *et al*. PPP1R15A-expressing monocytic MDSCs promote immunosuppressive liver microenvironment in fibrosis-associated hepatocellular carcinoma. *JHEP Rep* 2024;6(7):101087. doi:10.1016/j.jhepr.2024.101087, PMID:38882672.
- [24] Liao TC, Huang JP, Tsai YT, Shih WC, Juan CC, Hsieh PS, *et al*. Granulocytic MDSC with Deficient CCR5 Alleviates Lipogenesis and Inflammation in Nonalcoholic Fatty Liver Disease. *Int J Mol Sci* 2022;23(21):13048. doi:10.3390/ijms232113048, PMID:36361830.
- [25] Zheng Y, Wang S, Wu J, Wang Y. Mitochondrial metabolic dysfunction and non-alcoholic fatty liver disease: new insights from pathogenic mechanisms to clinically targeted therapy. *J Transl Med* 2023;21(1):510. doi:10.1186/s12967-023-04367-1, PMID:37507803.
- [26] Pei K, Gui T, Kan D, Feng H, Jin Y, Yang Y, *et al*. An Overview of Lipid Metabolism and Nonalcoholic Fatty Liver Disease. *Biomed Res Int* 2020;2020:4020249. doi:10.1155/2020/4020249, PMID:32733940.
- [27] Jian SUN, Jiming Z. Advance in myeloid-derived suppressor cells. *Journal of Microbes and Infections* 2022;17(6):386–394. doi:10.3969/j.issn.1673-6184.2022.06.007, PMID:36915804.
- [28] Moayedfard Z, Sani F, Alizadeh A, Bagheri Lankarani K, Zarei M, Azarpira N. The role of the immune system in the pathogenesis of NAFLD and potential therapeutic impacts of mesenchymal stem cell-derived extracellular vesicles. *Stem Cell Res Ther* 2022;13(1):242. doi:10.1186/s13287-022-02929-6, PMID:35672797.
- [29] Wu J, Zheng L, Mo J, Yao X, Fan C, Bao Y. Protective Effects of MitoTEMPO on Nonalcoholic Fatty Liver Disease via Regulating Myeloid-Derived Suppressor Cells and Inflammation in Mice. *Biomed Res Int* 2020;2020:9329427. doi:10.1155/2020/9329427, PMID:32802885.
- [30] Wang X, Zhang L, Dong B. Molecular mechanisms in MASLD/MASH-related HCC. *Hepatology* 2025;82(5):1303–1324. doi:10.1097/hep.000000000000786, PMID:38349726.
- [31] Yao L, Abe M, Kawasaki K, Akbar SM, Matsuura B, Onji M, *et al*. Characterization of Liver Monocytic Myeloid-Derived Suppressor Cells and Their Role in a Murine Model of Non-Alcoholic Fatty Liver Disease. *PLoS One* 2016;11(2):e0149948. doi:10.1371/journal.pone.0149948, PMID:26901500.
- [32] Zhou Z, Lai P, Zhang S, Wang Y, Qu N, Lu D, *et al*. The Relationship between Hepatic Myeloid-Derived Suppressor Cells and Clinicopathological Parameters in Patients with Chronic Liver Disease. *Biomed Res Int* 2021;2021:6612477. doi:10.1155/2021/6612477, PMID:33860040.
- [33] Suh YG, Kim JK, Byun JS, Yi HS, Lee YS, Eun HS, *et al*. CD11b(+) Gr1(+) bone marrow cells ameliorate liver fibrosis by producing interleukin-10 in mice. *Hepatology* 2012;56(5):1902–1912. doi:10.1002/hep.25817, PMID:22544759.
- [34] Höchst B, Mikulec J, Baccaga T, Metzger C, Welz M, Peusquens J, *et al*. Differential induction of Ly6G and Ly6C positive myeloid derived suppressor cells in chronic kidney and liver inflammation and fibrosis. *PLoS One* 2015;10(3):e0119662. doi:10.1371/journal.pone.0119662, PMID:25738302.
- [35] McCabe L, Burns JE, Latifoltojar A, Post FA, Fox J, Pool E, *et al*. MAVMET trial: maraviroc and/or metformin for metabolic dysfunction associated fatty liver disease in adults with suppressed HIV. *Aids* 2024;38(10):1513–1522. doi:10.1097/qad.0000000000003947, PMID:38819839.
- [36] Kern L, Mittenbühler MJ, Vesting AJ, Ostermann AL, Wunderlich CM, Wunderlich FT. Obesity-Induced TNF α and IL-6 Signaling: The Missing Link between Obesity and Inflammation-Driven Liver and Colorectal Cancers. *Cancers (Basel)* 2018;11(1):24. doi:10.3390/cancers11010024, PMID:30591653.
- [37] Clements VK, Long T, Long R, Figley C, Smith DMC, Ostrand-Rosenberg S. Frontline Science: High fat diet and leptin promote tumor progression by inducing myeloid-derived suppressor cells. *J Leukoc Biol* 2018;103(3):395–407. doi:10.1002/jlb.4hi0517-210r, PMID:29345342.
- [38] Zhang H, Lian M, Zhang J, Bian Z, Tang R, Miao Q, *et al*. A functional characteristic of cysteine-rich protein 61: Modulation of myeloid-derived suppressor cells in liver inflammation. *Hepatology* 2018;67(1):232–246. doi:10.1002/hep.29418, PMID:28777871.
- [39] Bradshaw D, Abramowicz I, Bremner S, Verma S, Gilleece Y, Kirk S, *et al*. Hepmarc: A 96 week randomised controlled feasibility trial of add-on maraviroc in people with HIV and non-alcoholic fatty liver disease. *PLoS One* 2023;18(7):e0288598. doi:10.1371/journal.pone.0288598, PMID:37450478.
- [40] Xia S, Sha H, Yang L, Ji Y, Ostrand-Rosenberg S, Qi L. Gr-1+ CD11b+ myeloid-derived suppressor cells suppress inflammation and promote insulin sensitivity in obesity. *J Biol Chem* 2011;286(26):23591–23599. doi:10.1074/jbc.M111.237123, PMID:21592961.
- [41] Li Y, Li N, Liu J, An X. Gr-1(high)Ly6G(+)Myeloid-derived suppressor cells and their role in a murine model of non-alcoholic steatohepatitis. *Am J Transl Res* 2020;12(6):2827–2842. PMID:32655813.
- [42] Yao S, Yang X, An J, Jin H, Wen G, Wang H, *et al*. Role of the S100 protein family in liver disease (Review). *Int J Mol Med* 2021;48(3):166. doi:10.3892/ijmm.2021.4999, PMID:34278437.
- [43] Fang Z, Liu C, Cheng Y, Ji Y, Liu C. Combined analysis of bulk, single-cell RNA sequencing, and spatial transcriptomics reveals the expression patterns of lipid metabolism and ferroptosis in the immune microenvironment of metabolic-associated fatty liver disease. *Life Sci* 2025;362:123377. doi:10.1016/j.lfs.2025.123377, PMID:39793853.
- [44] Li Z, Luo G, Gan C, Zhang H, Li L, Zhang X, *et al*. Spatially resolved multi-omics of human metabolic dysfunction-associated steatotic liver disease. *Nat Genet* 2025;57(12):3112–3125. doi:10.1038/s41588-025-02407-8, PMID:41286103.