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Inflammation in MASLD progression and cancer

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Summary

Steatotic liver diseases include metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-associated liver disease, and metabolic dysfunction and alcohol-related liver disease (MetALD), encompassing a spectrum of metabolic liver disorders that range from steatosis to steatohepatitis, cirrhosis, and hepatocellular carcinoma. Steatotic liver disease is primarily driven by alcohol consumption and metabolic dysfunction, making it the leading cause of chronic liver disease. Steatosis is defined by excessive fat accumulation in the liver without significant liver injury or inflammation. In contrast, inflammation is the predominant factor that drives the progression of steatosis to steatohepatitis and, ultimately, to cancer. In this review, we summarise the current understanding of the inflammatory mechanisms underlying the pathogenesis of MASLD and explore molecular targets that may offer the potential for pharmacological intervention. Additionally, given the pathological similarities between MASLD and MetALD, relevant inflammatory pathways in MetALD are briefly discussed to underscore both commonalities and key distinctions between the two conditions.

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Introduction

Aberrant fat accumulation in the liver is a hepatic manifestation of metabolic syndrome. The recent surge in the prevalence of metabolic syndrome has accelerated the incidence of steatotic liver diseases, including metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-associated liver disease (ALD), and metabolic dysfunction and alcohol-related liver disease (MetALD).[1,2] In the past, viral hepatitis was the primary cause of chronic liver disease; however, effective antiviral treatment and vaccination have remarkably reduced the contribution of viral infection to chronic liver diseases, while MASLD, ALD, and MetALD have become the leading causes of end-stage liver disease.

MASLD includes a range of metabolic liver diseases, such as steatosis, steatohepatitis, cirrhosis, and hepatocellular carcinoma (HCC). MASLD arises from excessive caloric intake and metabolic dysregulation within the liver, with its pathogenesis strongly linked to obesity and insulin resistance, which markedly promote fatty acid synthesis in the liver. Simple steatosis is a prevalent medical condition, with approximately 25% of the adult population assumed to be affected.[3] As the initial phase of MASLD, simple steatosis is normally benign. However, approximately 25% of individuals with simple steatosis progress to metabolic dysfunction-associated steatohepatitis (MASH), which is the more aggressive form of steatosis, facilitated by multiple factors involved in inflammation.

Liver cancer is a highly aggressive disease with limited treatment options. Primary liver cancer consists of HCC, which accounts for 80% of cases, and intrahepatic cholangiocarcinoma, comprising approximately 15% of cases. MASLD is a significant risk factor for HCC development. Approximately 20% of individuals with MASH progress to cirrhosis,[4] which is a strong risk factor for HCC development. Furthermore, the estimated annual rate of progression of MASH to HCC is approximately 2%. Primary liver cancer is the sixth most commonly diagnosed cancer worldwide and the third leading cause of cancer-related mortality.[5] Historically, viral hepatitis was the main risk factor for HCC; however, improvements in lifestyle and living standards have led to a surge in cases of MASLD, which is now emerging as the fastest-growing contributor to the incidence of liver cancer.[6] Therefore, understanding the inflammatory processes implicated in the progression of MASLD is crucial for identifying a therapeutic target amenable to medical intervention.

The Delphi consensus process led to the adoption of steatotic liver disease as a replacement for fatty liver disease and introduced MASLD as the new term for non-alcoholic fatty liver disease.[7] This updated nomenclature aims to improve diagnostic precision, reduce stigmatisation, and enhance disease classification. Additionally, a new category, MetALD, was established to encompass individuals whose alcohol consumption exceeds the previously defined threshold for non-alcoholic fatty liver disease but does not fit within the existing classification system. MetALD is characterised by a daily alcohol intake of 20–50 g for females and 30–60 g daily for males. Within this spectrum, some individuals exhibit conditions more closely aligned with MASLD, while others present with characteristics more typical of ALD. ALD is a spectrum of liver disorders caused by chronic excessive alcohol consumption, ranging from simple steatosis to more severe

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Keypoints

- The progression of metabolic dysfunction-associated steatotic liver disease (MASLD), a major cause of chronic liver disease linked to obesity and insulin resistance, from steatosis to severe conditions like steatohepatitis, cirrhosis, and hepatocellular carcinoma (HCC) is largely driven by inflammatory processes.
- Hepatic accumulation of harmful lipids leads to organelle dysfunction, oxidative stress, and lipotoxicity, which activate immune responses involving damage-associated molecular patterns and inflammatory signalling pathways, contributing to MASLD progression.
- Chronic inflammation and fibrosis, hallmarks of advanced MASLD, are mediated by immune cells, such as macrophages, neutrophils, T cells, and B cells, which secrete pro-inflammatory cytokines and exacerbate liver damage.
- Inflammation-driven microenvironment changes in advanced MASLD create conditions favourable for cancer development, with genetic mutations and signalling pathways, such as STAT3 activation, promoting the transition to MASLD-related HCC.
- The gut-liver axis facilitates bidirectional communication through bile acids and gut microbiota. Gut dysbiosis, driven by dietary factors, damages the gut barrier, enabling endotoxins, such as lipopolysaccharides, to enter the liver, triggering inflammation and accelerating MASLD.
- Obesity-related adipocyte death releases free fatty acids and inflammatory cytokines, exacerbating insulin resistance, lipid accumulation, and hepatic inflammation. Adipokines like leptin and adiponectin further influence liver fibrosis and immune responses.
- Emerging treatments for MASLD target pathways involved in inflammation and metabolism. However, various therapeutic approaches face obstacles to their clinical efficacy, highlighting the need for deeper insights into inflammatory mechanisms and metabolic regulation in liver diseases.
- Metabolic dysfunction and alcohol-related liver disease (MetALD) is a distinct liver condition characterised by the interplay of metabolic dysfunction and high alcohol consumption, with inflammation playing a central role in its progression, driven by immune cell activity, gut-liver axis disruptions, and adipose tissue alterations.

conditions such as alcohol-associated hepatitis, fibrosis, cirrhosis, and HCC. Persistent alcohol intake induces hepatocellular damage through oxidative stress, inflammation, and gut microbiota dysbiosis, leading to immune system activation and progressive liver injury.

In this review, we discuss the involvement of inflammation in the development of MASLD and MASLD-related HCC, and briefly discuss inflammation in MetALD. Inflammatory pathways in ALD have recently been reviewed in several articles,[2,8] and are not discussed in the current review. The liver is an immunological organ that accommodates a vigorous innate immune system involving multiple types of immune cells, such as macrophages, neutrophils, T cells, B cells, and dendritic cells, whose participation in the progression of MASLD is discussed in the current article. The inflammatory processes involved in the development of MASLD are not only driven by hepatocyte injury and the infiltration and activation of immune cells in the liver but also by the crosstalk with other organs, such as the gut and adipose tissues.[9] Therefore, we elaborate on the contribution of pathological changes in adipose tissues and the gut microbiome to the progression of MASLD. Similarly, MetALD pathogenesis is characterised by aberrant fat deposition in the liver, associated with alcohol consumption or metabolic dysregulation, which disrupts fatty acid β-oxidation and facilitates lipogenesis in hepatocytes. Moreover, inflammatory processes play key roles in its progression. Therefore, the current article also briefly discusses how inflammatory processes are implicated in the development of MetALD.

Pathogenesis of MASLD and MASLD-related cancer

Steatosis, the initial phase of a spectrum of metabolic liver diseases that constitute MASLD, is a medical condition characterised by excessive fat accumulation in hepatocytes. In steatotic livers, lipid droplets are present in more than 5% of hepatocytes. *De novo* lipogenesis is a significant contributor to this excess fatty acid accumulation in MASLD, alongside other sources such as adipose tissue and dietary lipids. MASLD is frequently associated with obesity and diabetes, conditions marked by insulin resistance that enhance the lipolysis of fatty acids in adipose tissues. Notably, insulin-induced *de novo* lipogenesis persists even under insulin-resistant conditions,[10] thereby accelerating fat accumulation in the liver.

The liver has a robust defence system to prevent an accumulation of harmful free fatty acids (FFAs). For example, fatty acids can be converted into triglycerides through the action of multiple enzymes, such as diacylglycerol O-acyltransferases.[11] In addition, mitochondrial β-oxidation transforms fatty acids into acetyl-CoA. Moreover, hepatic triglycerides can be secreted into the bloodstream as very-low-density lipoprotein. Under normal conditions, there is a balance between the supply and clearance of hepatic lipids. However, under pathological conditions conducive to MASLD development, these defence mechanisms are typically overwhelmed, leading to the accumulation of FFAs.[9] The accumulation of fatty acids promotes cellular stress, termed lipotoxicity. FFAs may enhance the production of other lipotoxic lipids, such as ceramides and sphingolipids, whose production is elevated in MASLD. Cholesterol is another lipotoxic lipid that has recently drawn attention as a significant factor stimulating MASH development.[12]

Liver injury and inflammation

Hepatic accumulation of harmful lipids causes dysfunction of intracellular organelles, including the endoplasmic reticulum (ER) and mitochondria in hepatocytes. For example, saturated fatty acids (SFAs) such as palmitate (C16:0) and stearate (C18:0) alter ER homeostasis.[13] Because the ER plays a fundamental role in secretory and transmembrane protein

folding, the accumulation of misfolded proteins due to SFAs activates unfolded protein response stress sensors to restore ER function. Unfolded protein response stress sensors are composed of IRE1 (inositol-requiring enzyme 1), PERK (PKR-like ER kinase), and activating transcription factor 6.[13] Prolonged activation of PERK and IRE1 in hepatocytes leads to hepatocyte death via the induction of C/EBP homologous protein and the pro-apoptotic c-Jun N-terminal kinase signalling pathway, respectively.[14] In addition to ER stress-mediated hepatic injury, SFAs cause hepatocyte death via reactive oxygen species (ROS) overproduction.[15] Cellular ROS production is closely related to mitochondrial respiration, which is linked to fatty acid β-oxidation.[16] Therefore, the increased flux of SFAs into mitochondria augments β-oxidation. In turn, ROS generation culminates in oxidative stress.[16] Hepatic mitochondrial respiration is adaptively elevated in response to increased flux of SFAs in obese individuals without MASH.[17] However, mitochondrial respiratory capacity is reduced in patients with MASH, along with a decline in antioxidant capacity.[17] Consequently, impaired mitochondrial function and diminished antioxidant defence may contribute to ROS-mediated oxidative stress, promoting MASH development.

During the progression from steatosis to MASH, various types of cell death including lipotoxicity-mediated lipoapoptosis, ferroptosis, necroptosis, and pyroptosis, trigger an inflammatory response by releasing damage-associated molecular patterns (DAMPs) from damaged hepatocytes. Subsequently, DAMPs stimulate the NLRP3 (NACHT, LRR, and PYD domains-containing protein 3) inflammasome in liver-resident macrophages, termed Kupffer cells (KCs).[18] NF-κB has been identified as a key transcription factor that upregulates the NLRP3 inflammasome and pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β in KCs.[18] Additionally, KCs and damaged hepatocytes produce various chemokines that recruit monocytes, neutrophils, and T lymphocytes into the liver, further stimulating the release of a wide range of pro-inflammatory cytokines and hepatotoxic factors.[19]

While chronic inflammation, characterised by immune cell infiltration with hepatic lipid accumulation, is a hallmark of MASH, fibrosis caused by hepatic stellate cell (HSC) activation is a key feature of advanced MASH. HSCs can be activated by multiple factors, which include DAMPs or NLRP3 inflammasome oligomers released by damaged hepatocytes, transforming growth factor-β (TGF-β) produced by KCs, and myeloperoxidase secreted by neutrophils.[18] When fibrosis begins to alter hepatic architecture, oxygen supply to the liver is reduced, resulting in compromised liver function.

Cancer

Continuous lipotoxicity-induced cell death is associated with chronic inflammation and fibrosis, creating a microenvironment that supports carcinogenesis. HCC is the most common type of primary liver cancer, likely originating from differentiated hepatocytes following multiple somatic mutations.[6] DNA damage and defective DNA repair can occur as a consequence of overwhelming oxidative stress in advanced MASH, resulting in active oncogenes or inactive tumour suppressor genes.[20] In addition, polymorphisms in *PNPLA3* (patatin-like phospholipase domain containing 3) contribute to the risk of MASH-related HCC.[21]

During the transition from MASH to HCC, TNF-α and IL-6 produced by inflammatory cells promote HCC development through STAT3 (signal transducer and activator of transcription 3) activation.[22] STAT3 activation may lead to CD44 expression in HCC-initiating cells, preventing cell death or cell cycle exit caused by DNA damage-induced p53 activation.[23] Accumulation of p62 and downregulation of carnitine palmitoyltransferase 2 also protect HCC-initiating cells from oxidative stress and lipotoxicity, respectively, in preneoplastic lesions.[24,25] Thus, HCC-initiating cells resist cell death in a lipotoxic environment and acquire multiple oncogenic mutations. MASH-related HCC is associated with a unique set of commonly mutated genes compared to HBV- and HCV-induced HCC, such as telomerase reverse transcriptase, β-catenin, and TP53.[6] A recent study revealed that a mutation in activin A receptor type 2A is more common in MASH-related HCC than in other HCC etiologies.[26] In addition, MASH-related HCC exhibits upregulation of numerous genes related to *de novo* lipogenesis, such as SREBP-1 (sterol regulatory element-binding protein 1), fatty acid synthase, acetyl-CoA carboxylase, ATP citrate lyase, and fatty acid translocase CD36.[27]

Interestingly, early-stage MASH-related HCC develops from a pro-inflammatory milieu. However, as the cancer progresses, the tumour microenvironment undergoes a transition into an immunosuppressive state.[28] This phenomenon is attributed to the expansion of pro-tumorigenic macrophages, neutrophils, myeloid-derived suppressor cells (MDSCs), and exhausted T cells.[29] Because the immunosuppressive microenvironment of MASH-related HCC notably differs from the microenvironment of virally induced HCC, immune checkpoint inhibitors appear to be less effective in patients with MASH-related HCC.[30] Hence, a comprehensive understanding of the distinct immunopathology of MASH-related HCC is important to improve therapeutic efficacy.

Inflammation in the development of MASLD and MASLD-related cancer

Role of immune cells

Inflammation is a key factor in the progression of MASLD, primarily orchestrated by the innate immune system. Immune cells contribute significantly to the pathogenesis of steatotic liver disease by mediating hepatocellular injury, inflammation, and fibrosis. In the early stages of MASLD, lipid accumulation in hepatocytes induces metabolic stress, triggering the activation of resident immune cells, particularly KCs, which subsequently release pro-inflammatory cytokines and chemokines. These mediators facilitate the recruitment of circulating immune cells, including monocyte-derived macrophages, neutrophils, and lymphocytes, thereby amplifying the inflammatory cascade. Moreover, dysregulated adaptive immunity further exacerbates disease progression, with T helper (Th) cells and regulatory T cells playing key roles in modulating the immune response.

This section discusses the role of various innate immune cells, including macrophages, neutrophils, dendritic cells (DCs), as well as adaptive immune cells, such as T and B cells, in mediating inflammation during the progression of MASLD (Table 1). The discussion initially focuses on macrophages and neutrophils, which are the first responders during the early phase of liver injury and inflammation, before expanding to the

Table 1. Involvement of immune cells in animal and human MASLD.

Immune cell type	Population change	Sample type		Function	Ref.
		Human	Mouse		
Neutrophils					
MPO-positive neutrophils	Increased	Patients with MASH (liver)		Contribution to MASH progression	42
			MCD-induced murine MASH (liver)	Contribution to MASH progression	175
Macrophages					
Liver-resident Kupffer cells	Decreased	Patients with MASLD (liver)		Possibly protective against MASH	176
	Decreased		MCD-induced murine MASH (liver)	Adaptation to lipid overload	31
Monocyte-derived Kupffer cells	Increased		MCD-induced murine MASH (liver)	Pro-inflammatory; Aggravation of MASH	31
Monocyte-derived macrophages	Increased	Patients with MASH (liver)		Pro-inflammatory	133,134
	Increased	Patients with MASLD (liver)		Pro-inflammatory; Aggravation of MASH	176
	Increased	Patients with MASH (liver)		Aggravation of MASH	80
	Increased		MCD- or WD-induced murine MASH (liver)	Pro-inflammatory; Aggravation of MASH	33,134
	Increased		NASH diet-induced murine MASH (liver)	Pro-inflammatory	177
$CD206^{lo}$ ESAM- KC1	Increased		HFD-induced murine MAFL (liver)	Unclarified	32
$CD206^{hi}$ $ESAM^{+}$ KC2	Increased		HFD-induced murine MAFL (liver)	Aggravation of MASH	32
$CD9^{+}$ $TREM2^{+}$ lipid-associated macrophages	Increased	Patients with MASH (liver)		Possibly protective against MASH	178
	Increased	Patients with MASH (liver)		Possibly protective against MASH	179
	Increased		AMLN- or CDHFD-induced murine MASH (liver)	Protective against MASH	178
	Increased		HFD-induced murine MASH (liver)	Anti-fibrotic; Protective against MASH	35,180
	Increased		WD-induced murine MASH (liver)	Protective against MASH	179
	Increased		Modified AMLN-induced murine MASH (liver)	Pro-inflammatory; Aggravation of MASH	181
$CD9^{+}$ $TREM2^{+}$ Scar-associated macrophages	Increased	Patients with cirrhosis (liver)		Profibrotic	36
$MerTK^{+}$ macrophages	Increased		FPC-induced murine MASH (liver)	Profibrotic	37
Tumour-associated macrophages	Increased	Patients with HCC (liver)		Immunosuppressive	182
	Increased	Patients with HCC (liver)		Immunosuppressive	76
	Increased		DEN/NASH diet-induced murine HCC (liver)	HCC progression	132

(*continued on next page*)

Table 1. (*continued*)

Immune cell type	Population change	Sample type		Function	Ref.
		Human	Mouse		
T lymphocytes					
$CD8^+$ T cells	Increased	Patients with MASLD (liver)		Aggravation of MASH	57
	Increased	Patients with MASH (liver)		Aggravation of MASH	75
	Increased		HFHC diet-induced murine MASH (liver)	Aggravation of MASH	58
CXCR6$^+$ $CD8^+$ PD-1$^+$ T cells	Increased	Patients with HCC (liver)		HCC progression	30
	Increased		CDHFD- or WD-induced murine MASH (liver)	Auto-aggressive; Aggravation of MASH	72
	Increased		CDHFD-induced murine HCC (liver)	HCC progression	30
$CD4^+$ Th cells	Decreased	Patients with MASH (liver)		Anti-tumour immunity	73
	Decreased	Patients with HCC (liver)		Anti-tumour immunity	76
	Increased		WD-induced murine MASH (liver)	Aggravation of MASH	59
	Decreased		Myc/MCD-induced murine HCC (liver)	Anti-tumour immunity	73
Th1 $CD4^+$ T cells	Increased		HFD-induced murine MAFL (liver)	Pro-inflammatory; Aggravation of MASH	183
Th17 $CD4^+$ T cells	Increased	Patients with MASLD (liver)		Aggravation of MASH	62
	Increased	Patients with MASLD (liver)		Pro-inflammatory; Aggravation of MASH	184
	Increased	Patients with MASLD (liver)		Aggravation of MASH	185
	Increased		MCD- or WD-induced murine MASH (liver)	Pro-inflammatory; Aggravation of MASH	184
Th22 $CD4^+$ T cells	Increased		MCD-induced murine MASH (liver)	Protective against MASH	186
Tregs	Increased	Patients with HCC (liver)		Immunosuppressive	74
	Increased	Patients with HCC (liver)		Immunosuppressive	76
	Decreased		HFD-induced murine MAFL (liver)	Anti-inflammatory	65
iNKT cells	Increased		MCD- or HF and high-carbohydrate (HFHC) diet-induced murine MASH (liver)	Aggravation of MASH	58,67
	Increased		CDHFD-induced murine HCC (liver)	HCC progression	75
γδ T cells	Increased		HFD- or MCD- or modified AMLN-induced murine MASH (liver)	Aggravation of MASH	66,68,187
MAIT cells	Increased in fibrotic septa	Patients with fibrosis or cirrhosis (liver)		Profibrotic	71
	Increased in fibrotic septa	Patients with cirrhosis (liver)		Profibrotic	188
	Increased		MCD-induced murine MASH (liver)	Protective against MASH	70
B lymphocytes					
B cells	Increased	Patients with MASLD (liver)		Pro-inflammatory	79,189
B2 cells	Increased		MCD- or HFHC-induced murine MASH (liver)	Pro-inflammatory; Aggravation of MASH	79,189

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Table 1. (*continued*)

Immune cell type	Population change	Sample type		Function	Ref.
		Human	Mouse		
IgA$^+$ B cells	Increased	Patients with MASH (Intestine)		Profibrotic	80
	Increased		CDHFD- or WD-induced murine MASH (intestine)	Profibrotic	80
IgA$^+$ PD-L1$^+$ Plasma cells	Increased		MASH-related murine HCC (liver)	Immunosuppressive; HCC progression	81
Bregs	Increased	Patients with MASLD (liver)		Immunosuppressive	190
	Increased		HFD-induced murine MASH (liver)	Immunosuppressive	190
	Increased		NRASG12V/c-Myc-induced murine HCC (liver)	Immunosuppressive; HCC progression	190
Dendritic cells					
XCR1$^+$ cDC1 cells	Increased	Patients with MASH (liver)		Aggravation of MASH	82
	Increased		MCD- or CDHFD-induced murine MASH (liver)	Pro-inflammatory; Aggravation of MASH	82
	Increased		DEN/ALIOS diet-induced murine HCC (liver)	Anti-tumour immunity	53
CD103$^+$ cDC1 cells	Increased		MCD-induced murine MASH (liver)	Protective against MASH	83
CX3CR1$^+$ DC cells	Increased		MCD-induced murine MASH (liver)	Pro-inflammatory; Aggravation of MASH	84
Innate lymphoid cells					
NK cells	Increased		MCD-induced murine MASH (liver)	Anti-fibrotic; Protective against MASH	191
	Decreased	Patients with HCC (liver)		Anti-tumour immunity	74
ILC3	Increased		HFD-induced murine MASH (liver)	Protective against MASH	192

Bregs, regulatory B cells; cDC, conventional dendritic cell; CDHFD, choline-deficient high-fat diet; DEN, diethylnitrosamine; FPC, fructose-palmitate-cholesterol; HCC, hepatocellular carcinoma; HFD, high-fat diet; HFHC, high-fat, high-carbohydrate; ILC, innate lymphoid cell; iNKT, invariant NK T; MAIT, mucosal-associated invariant T; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MCD, methionine- and choline-deficient diet; NK, natural killer; Th, T helper; Tregs, regulatory T cells; WD, western diet.

roles of other innate and adaptive immune cells in the later stages of disease progression.

Macrophages

Macrophages play a critical role in the immune response throughout all stages of MASLD development. In the liver, tissue-resident macrophages known as KCs are the major source of various pro-inflammatory cytokines and chemokines, including TNF-α, IL-1β, and CCL2 (also known as MCP-1). A recent study unveiled that the population of liver-resident KCs is reduced during MASH; however, the pool of KCs is maintained by replenishment with monocyte-derived KCs (moKCs) that display more pro-inflammatory profiles than liver-resident KCs.[31] MoKCs are distinct from both resident KCs and infiltrating monocytes in their origin, function, and contribution to liver homeostasis and pathology. MoKCs originate from circulating monocytes that infiltrate the liver, particularly in response to liver injury, inflammation, or the depletion of resident KCs. In contrast, infiltrating monocytes are bone marrow-derived circulating immune cells that migrate into the liver following inflammatory signals but have not yet undergone differentiation into macrophages. Another study further dissected that KCs can be divided into KC1 ($CD206^{lo}ESAM^{-}$) and KC2 ($CD206^{hi}ESAM^{+}$) based on their transcriptomic signatures, with the latter subset potentially involved in the progression of MASH via CD36 expression.[32] Besides KCs, monocyte-derived macrophages (moMFs) that do not express classical KC markers play a pro-inflammatory role in aggravating MASH.[33] A distinct subset of monocytes gives rise to lipid-associated macrophages (LAMs) or MASH-associated macrophages expressing CD9 and TREM2 (triggering receptors expressed on myeloid cells 2).[34] The function of LAMs in MASLD development is controversial; however, a large body of evidence suggests that LAMs play a protective role against MASH.[35] $TREM2^{+}CD9^{+}$ macrophages are also known as scar-associated macrophages that localise in the fibrotic niche, where they produce pro-fibrogenic mediators, such as osteopontin and galectin 3.[36] Macrophages that express Mer tyrosine kinase promote fibrosis via HSC activation in MASH.[37]

During the transition from MASH to HCC, premalignant hepatocytes secrete CCL2, which recruits immune cells to eliminate them.[38] However, a subset of C–C chemokine receptor type 2 $(CCR2)^{+}$ moMFs contributes to the establishment of a microenvironment that impairs immune surveillance in the early phase of MASH-related HCC.[39] In addition, the advent of tumour-associated macrophages (TAMs) promotes an immunosuppressive microenvironment by triggering the exhaustion of $CD8^{+}$ T cells.[40] Recently, $IL\text{-}4I1^{+}$ TAMs in the periphery of HCC were found to promote the recruitment of regulatory T cells (Tregs) into tumours. How this novel subset of TAMs consistently plays a role in the context of MASH-related HCC remains elusive.

Neutrophils

Neutrophils are polymorphonuclear leukocytes that participate in innate immunity to maintain tissue homeostasis in response to infection and tissue damage. Neutrophils possess various characteristics that may contribute to MASLD pathogenesis (Fig. 1). For example, neutrophils produce ROS through oxidative bursts, which could damage hepatocytes and activate immune cells, including macrophages and HSCs. In addition, neutrophils undergo degranulation and release diverse proteins, such as myeloperoxidase, neutrophil elastase, and lipocalin-2.[41] Gain- and loss-of-function studies of the proteins released by neutrophils have revealed their involvement in MASLD pathogenesis.[42,43] In addition, neutrophil extracellular traps (NETs) play a critical role in MASLD pathogenesis. Van der Windt *et al.* reported that NETs promote inflammation and MASLD-related HCC in mice.[44]

Neutrophil numbers are elevated in the livers of patients with MASH, and the chemokines that recruit neutrophils, such as CXCL1, CXCL2, and IL-8, are upregulated compared to those in individuals with simple steatosis.[45] In addition, the neutrophil-to-lymphocyte ratio correlates with hepatocyte injury, inflammation, and fibrosis in patients with MASH.[46] Neutrophil depletion by an Ly6g-neutralising antibody protected against hepatic steatosis and attenuated the hepatic expression of inflammatory and fibrogenic genes in mice fed a high-fat diet (HFD).[47] Adenovirus-driven CXCL1 and IL8 overexpression promoted hepatic neutrophil infiltration and exacerbated liver injury, inflammation, and steatosis in HFD-fed mice.[48] These results support the contribution of neutrophils to the development of MASLD; however, the protective role of neutrophils against MASLD development has also been documented. Kim *et al.* reported that neutrophil depletion inhibited inflammation and fibrosis in the early phase.[49] In contrast, the reparative function of neutrophils is also impaired by cell depletion, thereby exacerbating diet-induced MASH in mice during the resolution phase.[49] Another study demonstrated that neutrophils orchestrate the resolution of inflammation and tissue repair through ROS-dependent development of reparative macrophages.[50]

Neutrophils infiltrate tumours and contribute to tumour progression through their functional plasticity. Tumour-associated neutrophils have been linked to poor prognosis in various cancers, with the neutrophil-to-lymphocyte ratio in the blood correlating with cancer severity.[51] Wang *et al.* demonstrated that NETs modulate the activity of Tregs via the metabolic reprogramming of naïve $CD4^{+}$ T cells, thereby enhancing the immunosuppressive microenvironment in the liver and stimulating cancer development.[52] Leslie *et al.* highlighted that neutrophils expressing C-X-C chemokine receptor (CXCR)2 are increased in MASH-related HCC.[53] Moreover, their studies revealed that combining a CXCR2 antagonist with anti-programmed death-1 (PD-1) therapy effectively reduced tumour burden and prolonged survival in models of MASH-related HCC that were unresponsive to immune checkpoint inhibition.[53] Serum amyloid A is a key inflammatory cytokine associated with resistance to anti-PD-1 therapy in HCC. He *et al.* reported that targeting $PD\text{-}L1^{+}$ neutrophils induced by serum amyloid A could offer a promising strategy to overcome anti-PD-1 resistance.[54] Conversely, neutrophils may exert antitumor functions by directly killing cancer cells and coordinating innate and adaptive immune responses.[55] This dual role of neutrophils in tumours may be attributed to their plasticity and heterogeneity.[55] The tumour microenvironment influences the polarisation of neutrophils to either N1 or N2.[56] N1 neutrophils possess pro-inflammatory and antitumour properties, while N2 neutrophils have anti-inflammatory and protumour properties. The specific functions of these distinct neutrophil populations remain largely unknown, especially in MASLD-

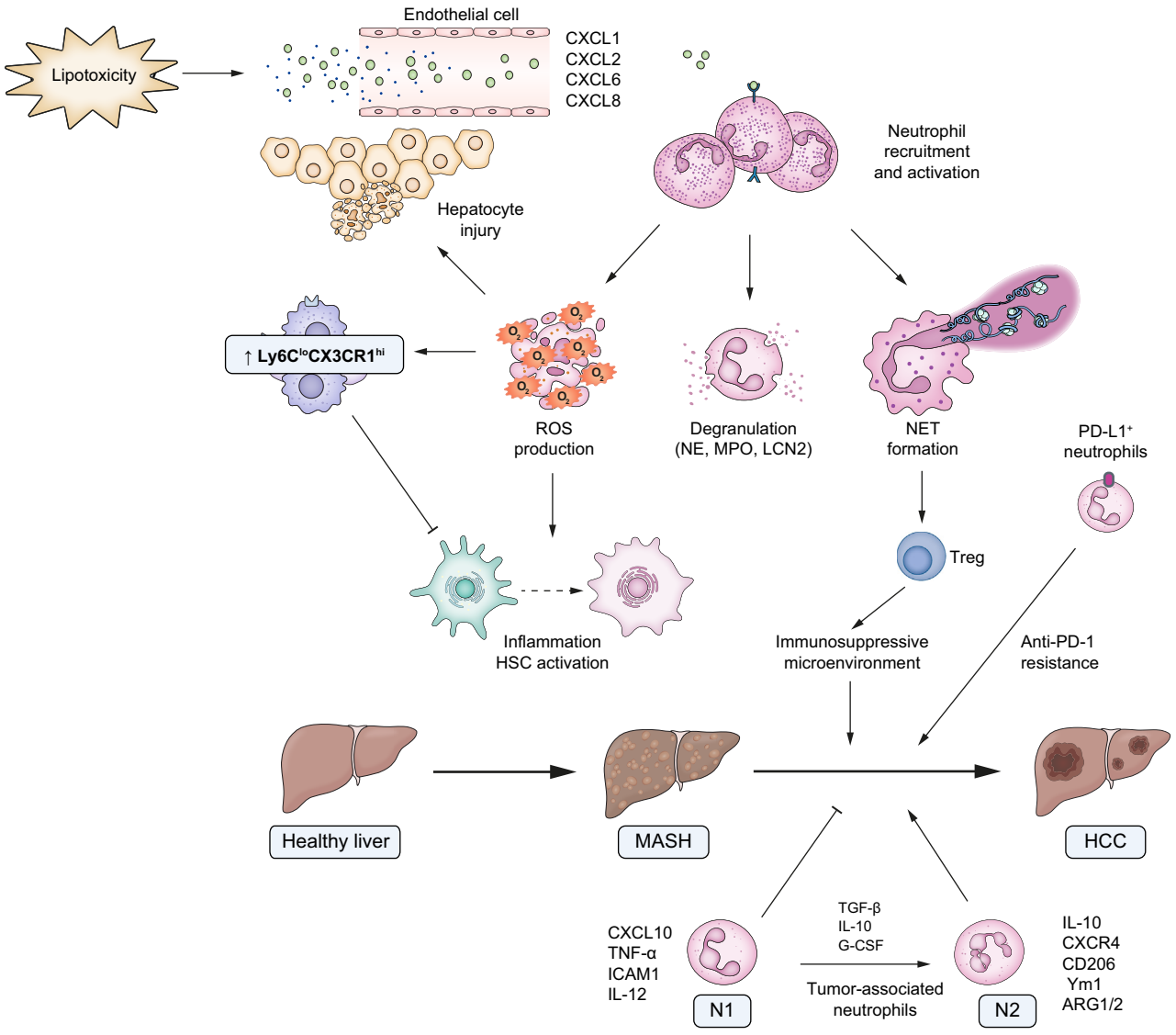


Fig. 1. Involvement of neutrophils in MASLD development. Lipotoxicity induces hepatocytes and endothelial cells to secrete chemokines, including CXCL1, CXCL2, CXCL6, and CXCL8 (IL-8), which recruit neutrophils to the liver. These activated neutrophils contribute to MASLD progression by promoting inflammation, HSC activation that releases ROS, and degranulation that releases neutrophilic proteins, such as neutrophil elastase. The formation of NETs contributes to HCC development. Additionally, TGF-β, IL-10, and G-CSF drive the polarisation of neutrophils towards the tumour-promoting N2 phenotype, further supporting HCC development. HCC, hepatocellular carcinoma; HSC, hepatic stellate cell; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NETs, neutrophil extracellular traps; ROS, reactive oxygen species.

related HCC, highlighting the need for further research in this area.

T lymphocytes

Conventional T cells and innate-like T cells (ILTs) are key contributors to inflammation in the development of MASLD (Fig. 2). Cytotoxic $CD8^+$ T cells are increased in patients with MASH.[57] However, depletion of these cells leads to reduced MASH progression in mice, suggesting that $CD8^+$ T cells may play pathological roles in MASH development.[58] In addition, the recruitment of $CD4^+$ T helper (Th) cells is observed in patients with MASH, implying the involvement of these cells in disease progression.[59] $CD4^+$ Th cells are particularly polarised to Th1 and Th17 subsets in MASH.[60] Th1 cells produce interferon-gamma that subsequently induces CXCL10, which recruits $CXCR3^+$ immune cells.[61] Th17 cells primarily produce pro-inflammatory cytokine IL-17 that aggravates inflammation and fibrosis.[62] In contrast, Th22 cells are reported to play protective roles in MASH by releasing IL-22.[63] Tregs directly suppress the functions of $CD8^+$ and $CD4^+$ T cells.[64] However, the number of Tregs is reduced, possibly due to their vulnerability to oxidative stress in MASLD.[65]

ILTs, including invariant natural killer T (iNKT) cells, γδ T cells, and mucosa-associated invariant T (MAIT) cells, are tissue-resident lymphocytes sharing properties with conventional T cells and innate immune cells. Fat-laden hepatocytes can

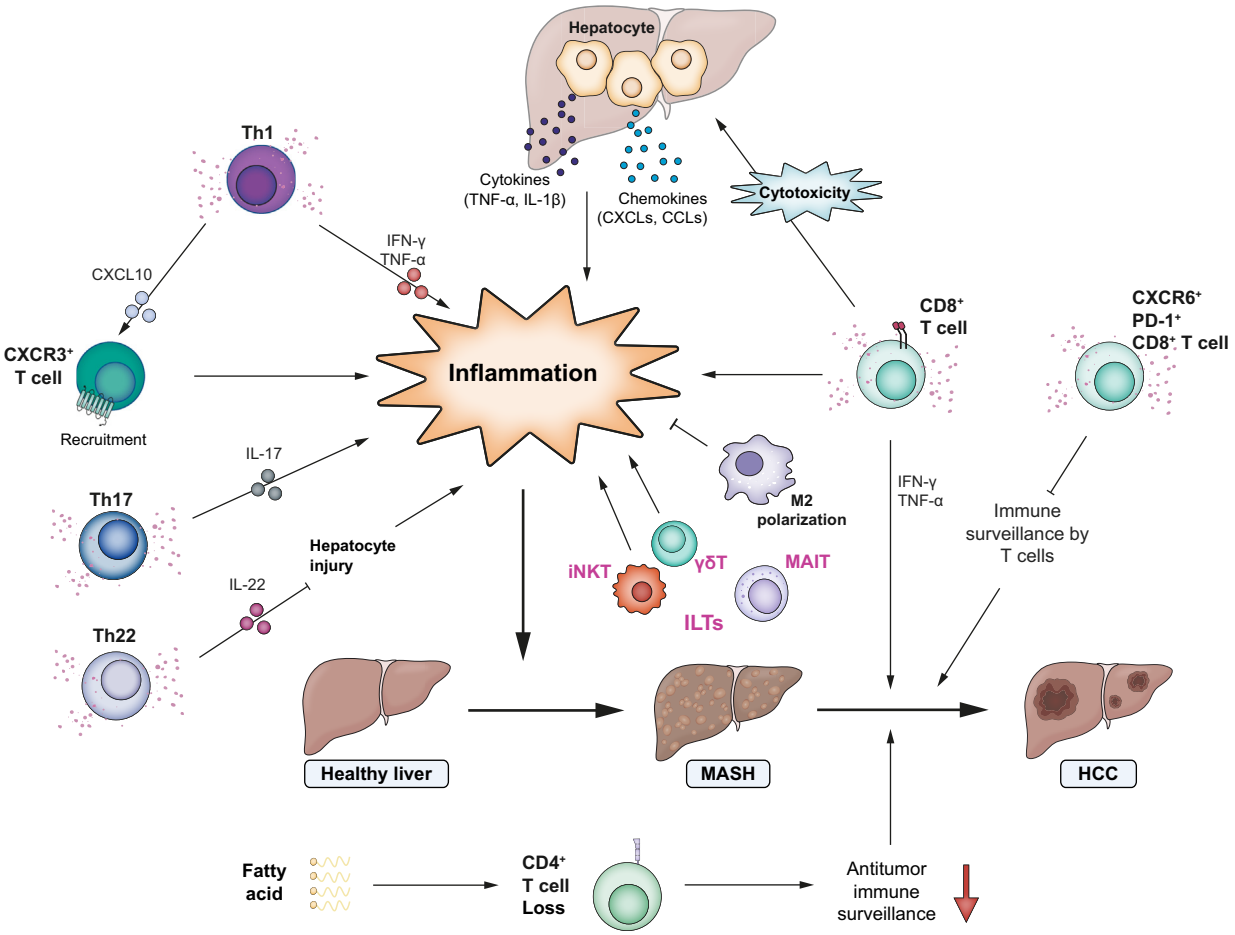


Fig. 2. Role of T cells in MASLD development. CD8⁺ T cells cause hepatocyte death and release cytokines, such as TNF-α and IFN-γ, thereby inducing inflammation. TNF-α and IFN-γ released by CD8⁺ T cells also stimulate tumour progression. Th1 cells promote inflammation by secreting TNF-α and IFN-γ, with IFN-γ-inducible CXCL10 recruiting CXCR3⁺ T cells to amplify the inflammatory response. Additionally, IL-17 produced by Th17 cells contributes to the inflammatory milieu. The presence of fatty acids results in the depletion of CD4⁺ T cells, impairs antitumor immune surveillance, and facilitates HCC progression. HCC, hepatocellular carcinoma; ILC, innate lymphoid cell; ILTs, innate-like T cells; iNKT, invariant NK T; MAIT, mucosal-associated invariant T; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; Th, T helper.

activate ILTs through NKG2D; once activated, ILTs secrete the pro-inflammatory cytokine IL-17.[66] The number of iNKT cells is increased in both human and mouse MASH.[67] However, the number of γδ T cells, another ILT subset, is increased in mice but not in patients with MASH.[68] In MASH progression, iNKT cells and γδ T cells play a pro-inflammatory role.[67,68] MAIT cell populations differ markedly between humans and mice. In humans, MAIT cells represent up to 45% of the liver T-cell population, while in mice, they are significantly less common, accounting for only about 1%.[69] Interestingly, an increase in MAIT cells is considered protective, as they help polarise macrophages into an anti-inflammatory phenotype,[70] while MAIT cells promote liver fibrosis by increasing pro-fibrogenic MoMFs.[71]

In MASH-related HCC, the pro-inflammatory milieu is progressively transformed by both cancer cells and immune cells into an immunosuppressive microenvironment. The emergence of CXCR6⁺CD8⁺PD-1⁺ T cells contributes to increased tumour burden by impairing the immunosurveillance function of cytotoxic T cells.[30] Pfister *et al.* observed that anti-PD-1 therapy increased the incidence of MASH-related HCC, accompanied by an increase in both the number and size of tumour nodules in mice.[30] This effect could be linked to the elevated presence of hepatic CXCR6⁺CD8⁺PD-1⁺ T cells. Furthermore, the anti-PD-1-induced development of HCC was mitigated by CD8⁺ T-cell depletion, indicating that CD8⁺ T cells play a pivotal role in the progression of MASH-related HCC. Similarly, CXCR6⁺CD8⁺ T cells are induced by IL-15 in the livers of mice with MASH.[72] The presence of IL-15 and acetate enhances the auto-aggressive property of CXCR6⁺CD8⁺ T cells, which can be defined as the ability of T cells to cause non-specific cytotoxicity.[72] Their acquisition of an auto-aggressive phenotype causes hepatocyte death independently of MHC class I and may enhance the emergence of steatohepatits.[30,72] Another mechanism that potentially promotes tumour growth in MASH involves the selective loss of CD4⁺ Th cells due to fatty acid-induced oxidative stress, which compromises antitumour surveillance.[73] In contrast to the reduction in CD4⁺ Th cells, Tregs accumulate within the tumour microenvironment.[74] Moreover, iNKTs are known to promote the development of MASH-related HCC by releasing pro-tumorigenic cytokines.[75]

The contribution of complex cellular networks in the pathogenesis of MASH-related HCC has recently been highlighted.

Li *et al.* established imaging mass cytometry that constructed a spatially resolved single-cell atlas from the liver tissue sections of patients with MASH-related HCC and healthy individuals, which enabled the analysis of intercellular networks involving a variety of immune cells.[76] This study suggested that the interaction of effector T cells with MDSCs and TAMs underlies the immunosuppression observed in MASH-related HCC, implicating MDSCs and TAMs as major contributors to T-cell exhaustion and immune evasion in MASH-related HCC.[76]

B lymphocytes

B cells play a multifaceted role in the development of MASLD by generating immunoglobulins and cytokines. B cells can be divided into B1 and B2 subsets by Th cell dependency.[77] Activation of B2 cells requires $CD4^+$ Th cells to produce highly antigen-specific IgA, IgG, and IgE.[64] However, B1 cells are known to produce IgM natural antibodies independently of $CD4^+$ Th cells.[78] In human and mouse MASH, the B2 subset is increased concomitantly with serum B cell-activating factor levels.[79] B cell-activating factor is a cytokine that controls the survival and maturation of B2 cells but not those of B1 cells. In the early phase of MASH, B2 cells are activated by oxidative stress-derived epitopes that subsequently influence the production of anti-oxidative stress-derived epitope IgG and pro-inflammatory cytokines, including IL-6 and TNF-α, thereby sustaining chronic inflammation.[79] In addition, IgA^+ B cells are known to promote the initiation of fibrosis in MASH through the activation of moMFs.[80]

In advanced MASH, B cells contribute to hepatocarcinogenesis by differentiating into immunosuppressive plasma cells. Mechanistically, TGF-β converts IgM^+ B cells into IgA^+ $PD\text{-}L1^+$ cells that suppress the cytotoxic activity of $CD8^+$ T cells by secreting IL-10.[81] Regulatory B cells are also known to suppress antitumour immunity by producing IL-10.[77]

Other immune cells

DCs are professional antigen-presenting cells that capture antigens and present them to T cells, linking innate and adaptive immunity. The heterogeneity of liver DC subsets may explain the controversial role of DCs in the development of MASLD. Conventional DCs (cDCs) can be divided into cDC1 and cDC2, and cDC1 is further subdivided into $XCR1^+$ cDC1 and $CD103^+$ cDC1 subsets.[69] The $XCR1^+$ cDC1 subset is abundant and promotes MASH, whereas the $CD103^+$ cDC1 subset is protective against MASH.[82,83] In addition, $CX_3CR_1^+$ DCs, derived from monocytes, promote MASH progression through TNF-α production.[84] In MASH-related HCC, DCs fail to generate a T cell-mediated antitumour effect in the immunosuppressive tumour microenvironment.[85]

Innate lymphoid cells (ILCs) are non-T, non-B lymphocytes that lack adaptive antigen receptors. ILCs are functionally and transcriptionally similar to $CD8^+$ and $CD4^+$ T cells.[86] During MASH progression, NK cells play an antifibrotic role by regulating macrophage polarisation.[87] Whether the ILC1 subset is protective or deleterious in MASH is controversial. The ILC3 subset may play a protective role in MASH by producing IL-22.[86] The role of ILCs in MASH-related HCC is also unclear, possibly due to difficulties in accurately distinguishing ILC subsets. NK cells exhibit antitumour activity; however, their immune surveillance functions are impaired within an immunosuppressive tumour microenvironment.[86]

Role of the microbiome

The gut-liver axis functionally and structurally connects the gut and liver. The liver releases multiple bioactive mediators, including bile acids (BAs), into the intestine, where gut microbiota metabolise endogenous substrates, such as BAs and amino acids, and exogenous substrates, including dietary metabolites. The liver and gut communicate bidirectionally by exchanging products.[88]

MASLD progression is affected by the gut microbiota,[89] which comprise numerous bacterial species, including Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia. These are essential for maintaining the integrity of the gut barrier and energy balance.[90] The dysregulation of microbiota, known as gut dysbiosis, disrupts metabolite regulation, lipid metabolism, and the integrity of the gut barrier, thereby contributing to the development of various liver diseases, including MASLD (Fig. 3).[91] Decreased amounts of bacterial DNA from the *Lachnospiraceae* family are associated with severe phenotypes, and Proteobacteria DNA was associated with lobular and portal inflammation scores.[92]

HFD or high-carbohydrate diets disrupt gut microbiota balance, damaging the intestinal barrier.[93,94] Gut dysbiosis may suppress the expression of proteins essential for maintaining intestinal tight junction integrity. The inhibition of junctional adhesion molecules further compromises the barrier, leading to an increased translocation of endotoxins, such as lipopolysaccharide (LPS), from the intestine into the bloodstream.[95] These endotoxins interact with pattern recognition receptors, including Toll-like receptors (TLRs), triggering the secretion of inflammatory cytokines and initiating inflammatory responses. Increased translocation of intestinal bacteria is frequently observed in MASLD and HCC. Dapito *et al.* demonstrated that while intestinal microbiota and TLR4 activation are not essential for HCC initiation, they are crucial for HCC promotion, thereby providing a mechanistic insight into how the intestinal microbiota influences HCC development.[96] LPS stimulates TLR4 on KCs to activate the NF-κB pathway and produce inflammatory cytokines.[97] In summary, endotoxins entering the bloodstream may translocate to the liver, contributing to inflammation and accelerating the progression of MASLD.

BAs play an important role in mediating gut-liver crosstalk by undergoing enterohepatic circulation.[98] Synthesised as the end products of hepatic cholesterol metabolism, BAs are transported via the biliary tract and transferred to the small intestine.[99] Approximately 95% of intestinal BAs are reabsorbed into the hepatic portal vein, while a fraction enters systemic circulation, where they function as signalling molecules.[100]

BAs activate the farnesoid X receptor (FXR) in various tissues, including the gut and the liver, to regulate the transcription of target genes involved in energy metabolism. FXR activation may reduce hepatic fat content by inhibiting hepatic *de novo* lipogenesis and stimulating fatty acid β-oxidation. Clifford *et al.* reported that deletion of the *Fxr* gene increased the level of hepatic triglycerides, and pharmacological activation of FXR alleviated MASLD by reducing hepatic triglyceride synthesis and intestinal lipid absorption.[101] FXR transactivates

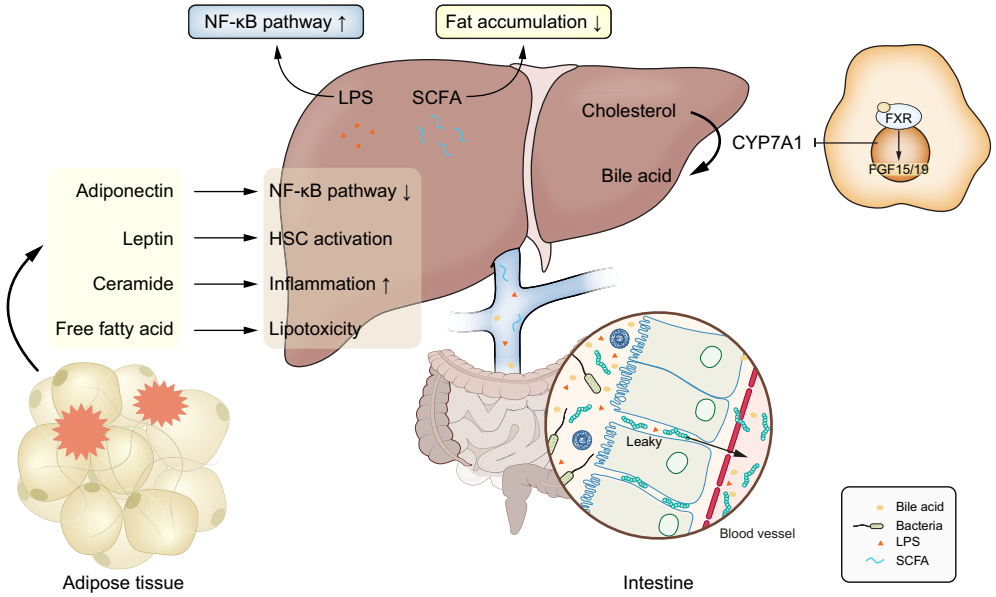


Fig. 3. Crosstalk between the liver and other organs. Gut dysbiosis compromises intestinal barrier integrity, leading to increased permeability. This disruption facilitates the translocation of bile acids, bacteria, LPS, and SCFAs across the intestinal barrier. Bile acids interact with receptors, such as FXR and GPBAR1. FXR activation by bile acids suppresses the expression of CYP7A1, a key enzyme in converting cholesterol to bile acids, through the FGF15/19 signalling pathway. LPS and SCFAs that translocate into the liver activate inflammatory responses and reduce fat accumulation, respectively. Adipokines, such as adiponectin and leptin, also exert significant effects on liver function. In addition, ceramides exacerbate hepatic inflammation by stimulating the release of pro-inflammatory cytokines. HSC, hepatic stellate cell; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids.

fibroblast growth factor (FGF) 15 and FGF19, thereby downregulating CYP7A1, which mediates the conversion of cholesterol to BAs.[102–104] Elevated BA levels have been observed in patients with MASLD, and FXR activation by BAs upregulates SHP (small heterodimer partner), which inhibits CYP7A1 transactivation.[105,106] CYP7A1 inhibition suppresses the conversion of cholesterol to BAs, resulting in hepatic cholesterol accumulation and lipotoxicity.[107]

Short-chain fatty acids (SCFAs) such as acetate, propionate, butyrate, and valerate are metabolites produced by the gut microbiota.[108] SCFAs are produced from indigestible starch and fibre, and are transferred via the portal circulation to the liver, where they participate in glucose and lipid synthesis. The protective roles of SCFAs in MASLD development have been widely reported. Evidence suggests that SCFAs help preserve gut barrier integrity by modulating hypoxia-inducible factors, strengthening intestinal tight junctions, and regulating immune cell activity. In addition, SCFAs reduce hepatic cholesterol contents by enhancing CYP7A1 and activating cholesterol efflux-related genes (*e.g. ABCA1, ABCG5, ABCG8*).[109] Furthermore, SCFAs promote autophagy by activating peroxisome proliferator-activated receptor (PPAR)γ and uncoupling protein 2, thereby alleviating hepatic fat accumulation.[110] Lau *et al.* reported that valeric acid produced by *Lactobacillus acidophilus* attenuates the development of MASH-related HCC by interacting with hepatocytic surface receptor GPR41/43 and inhibiting the Rho-GTPase pathway.[111] Wei *et al.* revealed that pentadecanoic acid, a metabolite generated by *Parabacteroides distasonis* from dietary inulin, ameliorates the development of MASH.[112] Another study demonstrated that acetates generated by *Bifidobacterium pseudolongum* suppressed HCC by activating GPR43 and inhibiting the JAK1/STAT3 pathway.[113] Besides bacteria-generated chemicals, structural components of bacteria have also been suggested as a contributor to MASLD pathogenesis. Shen *et al.* reported that flagellin of *E. coli* induces TLR5/NF-κB-dependent TWIST1 activation and promotes endothelial to mesenchymal transformation of liver sinusoidal endothelial cells, which promotes MASLD pathogenesis.[114]

Glucagon-like peptide-1 (GLP-1), an incretin hormone secreted by L cells in the intestine, plays a key role in regulating postprandial blood glucose levels. The gut microbiota influences GLP-1 production through metabolites such as SCFAs, BAs, and 2-oleoyl glycerol.[115] Specifically, SCFAs activate GPR41 and GPR43, BAs activate TGR5, and 2-oleoyl glycerol activates GPR119, collectively enhancing GLP-1 secretion. GLP-1 receptor (GLP-1R) agonists have shown promise as therapeutic agents for MASLD based on encouraging clinical trial data. Given that GLP-1R activity is modulated by the gut microbiota, the successful clinical development of GLP-1R agonists may depend significantly on the strategic utilisation of microbiota.

Recent studies have highlighted the possibility that gut microbiome signatures may serve as potential biomarkers for MASH and HCC.[116–118] These findings underscore the strong association between gut microbiota and the pathogenic mechanisms of MASH and HCC, highlighting their potential diagnostic value and therapeutic implications in MASLD.

Role of adipocyte death

Adipose tissue dysfunction plays a crucial role in driving systemic inflammation in MASLD. In individuals with MASLD, excessive adiposity, particularly in visceral fat, leads to adipocyte hypertrophy, hypoxia, and increased lipolysis, resulting in the release of FFAs into the circulation. These FFAs contribute to hepatic lipid accumulation and metabolic stress, exacerbating liver injury. Obesity and insulin resistance are key risk

factors for MASLD.[119] In obese individuals, adipocyte death is common and leads to unhealthy adipose tissue expansion, which releases adipokines and chemokines, contributing to insulin resistance.[120] Insulin resistance promotes hormone-sensitive lipase-mediated lipolysis in adipose tissue, increasing circulating fat.[121] Additionally, dying adipocytes release FFAs,[122] which are taken up by hepatocytes and induce lipotoxicity. FFAs impair hepatic insulin sensitivity and activate SREBP-1c and its downstream lipogenic genes, exacerbating liver fat accumulation. Beyond these metabolic disruptions, FFAs induce hepatocyte lipotoxicity and initiate inflammatory responses by releasing pro-inflammatory cytokines, activating the NF-κB pathway, and stimulating KCs.[123] Adipose tissue dysfunction and the resulting systemic inflammation establish a pathogenic link between obesity, metabolic dysregulation, and MASLD, making adipose tissue a critical target for therapeutic intervention in MASLD management.

Adipokines, including leptin and adiponectin, also modulate MASLD progression (Fig. 3). Leptin promotes HSC activation and liver fibrosis by inducing KCs to release TGF-β1.[124] In contrast, adiponectin offers protection against fibrosis by inhibiting HSC proliferation and inducing apoptosis in activated HSCs.[125] Adiponectin also suppresses the NF-κB pathway, reduces pro-inflammatory cytokine production (*e.g.* TNF-α), and increases production of anti-inflammatory cytokines like IL-10.[126] Ceramide, a sphingolipid involved in lipid metabolism, accumulates in obesity and is elevated by inflammatory cytokines, such as TNF-α, IL-1, and IL-6.[127] It is critical in mechanisms of insulin resistance, inflammation, oxidative stress, and cell death. Ceramide accumulation promotes adipocyte death, and ceramides released from injured adipocytes accumulate in hepatocyte mitochondria and the endoplasmic reticulum, inducing organelle stress, cell death, and inflammation.[128] Multiple factors released by injured adipocytes contribute to MASLD progression by triggering hepatocyte injury and immune cell activation. This systemic inflammatory state facilitates the recruitment of immune cells to the liver, where they further propagate inflammation, hepatocellular injury, and fibrosis.

The role of adipose-liver crosstalk has also been highlighted in the context of MASH-related HCC pathogenesis. A secretory protein neuregulin 4 (NRG4) is produced by adipose tissue and contributes to metabolic homeostasis in the liver.[129–131] NRG4 reduces MASH development by protecting hepatocytes from stress-induced injury. Zhang *et al.* reported that NRG4 signalling restrains the tumour-prone liver microenvironment and serves as a hormonal checkpoint for MASH-related HCC.[132]

Anti-inflammatory therapies

The pathophysiology of MASLD is complex, involving dysregulated lipid metabolism, immune cell infiltration, and chronic inflammation, which necessitates a multifaceted approach to treatment involving many pathogenic mechanisms. Many therapeutic agents are currently undergoing clinical evaluation to address these factors, focusing on liver inflammation, lipid dysregulation, and fibrosis (Table 2). This section discusses the classes of investigational agents that directly target the molecules involved in the inflammatory pathways of MASLD pathogenesis, such as CCR2/CCR5 antagonists. It also covers other agents that may indirectly mitigate inflammatory mechanisms of MASLD pathogenesis, including FXR agonists, PPAR agonists, FGF21 analogues, GLP-1R agonists, and thyroid hormone receptor-β (THR-β) agonists.

CCR2/CCR5 antagonists

The CCR2 and CCR5 pathways are key to recruiting monocytes and macrophages to the liver, exacerbating inflammation and fibrosis in MASLD.[133,134] Therefore, antagonism of CCR2 and CCR5 may directly inhibit the inflammatory mechanisms of MASLD pathogenesis, with CCR2 and CCR5 emerging as promising targets for MASH treatment. Dual antagonists targeting CCR2 and CCR5, such as cenicriviroc, have demonstrated efficacy by reducing macrophage infiltration and thereby attenuating the inflammatory response.[135,136] In a phase II study (NCT02217475), cenicriviroc improved liver histology without worsening steatohepatitis, highlighting its potential as a viable treatment option for MASH. In a phase III study (NCT03028740), cenicriviroc was found to be safe and well tolerated in patients with MASH and liver fibrosis. However, cenicriviroc did not demonstrate efficacy in treating liver fibrosis as assessed by histology in adults with MASH (NCT03028740).[137] The discrepancy between preclinical efficacy and clinical outcomes may be attributed to several factors, including the use of animal models that do not fully replicate the complex human disease conditions.

FXR agonists

Activation of FXR in hepatocytes reduces hepatic steatosis and inflammation, making it an attractive therapeutic target in MASH.[138] FXR activation inhibits inflammation through multiple indirect mechanisms, such as the reduction of cholestasis and the levels of toxic BAs. Obeticholic acid (OCA) reduces inflammation, likely through NF-κB modulation and the induction of anti-inflammatory macrophage phenotypes.[139] OCA reduced macrophage-driven liver inflammation and enhanced fibrosis resolution by modulating liver immune cells and hepatocytes.[140,141] In phase III clinical trials, OCA led to significant improvements in fibrosis and liver histology (NCT02548351). However, OCA was not approved by the US FDA despite showing promising efficacy in phase III clinical trials due to concerns over its safety profile and the need for further demonstration of its benefit-risk balance. While OCA demonstrated positive effects on liver histology, particularly in improving liver fibrosis and reducing MASH, the FDA raised concerns about the side effects of OCA, including pruritus, elevated cholesterol levels, and potential long-term cardiovascular risks.[142] Tropifexor has been shown to reduce liver inflammation and lead to histological improvements in phase II trials (NCT02855164). Similarly, the efficacy of cilofexor has been demonstrated in animal models and phase II clinical trials (NCT02854605).

PPAR agonists

PPARα and PPARδ are key in controlling fatty acid oxidation and lipogenesis, while PPARγ supports anti-inflammatory macrophage polarisation.[143] Elafibranor, a dual PPARα/δ agonist, has been shown to reduce hepatic steatosis, inflammation, and fibrosis in mice fed a choline-deficient high-fat diet.[144] Elafibranor enhanced fatty acid oxidation, reduced liver fat, and alleviated inflammation and fibrosis, improving histological outcomes in patients with MASH

Table 2. Clinical studies for the development of MASH therapeutics.

Drug class	Mechanism of action	Key drugs	Clinical trial results	Clinical trial identifier	Refs.
CCR2/CCR5 antagonists	Inhibits monocyte/macrophage recruitment, reduces inflammation	Cenicriviroc	Cenicriviroc (phase II): Improvement in liver histology without worsening steatohepatitis	NCT02217475	135,136,193
			Cenicriviroc (phase III): Safe, did not improve liver fibrosis	NCT03028740	
FXR agonists	Reduces hepatic steatosis and inflammation, modulates bile acid metabolism	Obeticholic acid, tropifexor, cilofexor	Obeticholic acid (phase III): Improvement in fibrosis and histology, rejected by FDA due to safety concerns	NCT02548351	139,142
			Tropifexor (phase II): Reduction in liver inflammation	NCT02855164	
			Cilofexor (phase II): Reduction in hepatic steatosis, liver biochemistry, and serum bile acids	NCT02854605	
PPAR agonists	Regulates lipid metabolism, promotes anti-inflammatory macrophage polarisation	Elafibranor	Elafibranor (phase II): Improvement in histology	NCT01694849	144
			Elafibranor (phase III): No efficacy, trial terminated	NCT02704403	
		Lanifibranor	Lanifibranor (phase II): Reduction in hepatic lipid accumulation and fibrosis	NCT03008070	
			Lanifibranor (phase III): Ongoing	NCT04849728	
FGF21 analogues	Reduces liver fat and inflammation	Pegbelfermin, efruxifermin, pegozafermin	Pegbelfermin (phase IIa): Reduction in liver fat	NCT02413372	146
			Pegbelfermin (phase IIb): Did not meet primary endpoint	NCT03486899	
			Efruxifermin (phase II): Reduction in the hepatic fat fraction, serum ALT levels and improvement in NAS (≥2 scores) without worsening of fibrosis	NCT03976401 NCT04767529	
			Pegozafermin (phase II): Reduction in liver fat, inflammation, and fibrosis	NCT04929483	
GLP-1R agonists	Stimulates insulin secretion, reduces glucagon, promotes weight loss	Liraglutide, semaglutide	Liraglutide (phase II): Reduction in liver fat and improvement in histology	NCT02654665	147
			Semaglutide (phase II): Reduction in inflammation	NCT02970942	
THR-β agonists	Regulates hepatic lipid metabolism, inhibits immune cell recruitment	Resmetirom	Resmetirom (phase III): Reduction in liver fat and inflammatory markers Approved by FDA as first MASH treatment	NCT03900429 NCT04197479	150

CCR, C–C chemokine receptor; FGF21, fibroblast growth factor 21; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; MASH, metabolic dysfunction-associated steatohepatitis; PPAR, peroxisome proliferator-activated receptor; THR-β, thyroid hormone receptor-β.

(NCT01694849). However, a phase III study (NCT02704403) was terminated after interim results showed no efficacy. Lanifibranor, a pan-PPAR agonist, also targets multiple pathways in MASH, effectively reducing liver lipid accumulation and fibrosis in phase II clinical trials (NCT03008070). A phase III study for lanifibranor is ongoing (NCT04849728).

FGF21 analogues

Recent research has highlighted the potential of FGF21 analogues in treating MASH by effectively reducing liver fat and inflammation.[145] Pegbelfermin, an FGF21 analogue, significantly reduced liver fat and improved liver histology in a phase IIa study (NCT02413372). However, a phase IIb study with pegbelfermin did not meet its primary endpoint (NCT03486899). Another FGF21 analogue, efruxifermin reduced liver fat and inflammation in preclinical models.[146] Efruxifermin has shown promise in phase II clinical trials (NCT03976401, NCT04767529). Additionally, pegozafermin, another FGF21 analogue, effectively reduced liver fat, inflammation, and fibrosis in phase II clinical trials for MASH (NCT04929483).

GLP-1R agonists

GLP-1R agonists stimulate insulin secretion, inhibit glucagon, and promote weight loss, improving hepatic steatosis and inflammation.[147] Liraglutide and semaglutide reduce liver fat and improve liver histology in patients with MASH. Clinical trials have demonstrated the efficacy of these agents in reducing inflammation and improving overall metabolic profiles, positioning them as a potential therapeutic option in MASH (NCT02654665, NCT02970942).

THR-β agonists

Activation of THR-β has been suggested to inhibit immune cell recruitment and mediate inflammation.[148] THR-β agonists target hepatic lipid metabolism without the systemic effects of thyroid hormones, making them particularly promising for treating MASH.[149] Resmetirom, a THR-β agonist, has been shown to significantly reduce liver fat and inflammatory markers in experimental MASH.[150] The US FDA has approved resmetirom as the first medication for MASH treatment following promising clinical results (NCT03900429, NCT04197479).

MetALD

Understanding MetALD

MetALD and MASLD share similarities as both are driven by metabolic dysfunction, which disrupts hepatic lipid metabolism, promotes hepatic fat accumulation, and ultimately leads to hepatocellular injury and inflammatory responses. MetALD represents a distinct category separate from pure MASLD, characterised by higher levels of alcohol intake. Its diagnosis is based on the presence of both metabolic dysfunction and alcohol consumption. According to the Delphi consensus, MetALD is defined as MASLD co-occurring with alcohol consumption exceeding 140–350 g/week for females and 210–420 g/week for males.[151] Within the group of patients with MetALD, the predominant driver may vary, with some cases being primarily influenced by MASLD and others by ALD. Alcohol consumption accelerates the progression of MASH, increasing the risk of liver decompensation.[152] The definition of MetALD emphasises the role of alcohol in disease progression. Although patients also exhibit metabolic dysfunction, the detrimental effects of alcohol cannot be overlooked. Alcohol exacerbates oxidative stress and hepatic inflammation, further accelerating liver injury progression.[2] MetALD provides new opportunities to investigate the interplay between alcohol and fat in the development of steatotic liver diseases.

Inflammation in MetALD

Both MASLD and MetALD involve inflammation, oxidative stress, mitochondrial dysfunction, and aberrant activation of the immune system. In MASLD, liver injury primarily results from metabolic dysregulation, whereas in MetALD, metabolic abnormalities are compounded by the direct hepatotoxic effects of alcohol. The metabolism of alcohol by the CYP2E1 pathway generates excessive ROS, inducing oxidative stress and mitochondrial damage, which in turn exacerbate hepatocyte apoptosis and inflammatory responses.[153] Additionally, due to the additional impact of alcohol, liver fibrosis progresses more rapidly in MetALD. Studies have shown that patients with MetALD are more likely to develop steatohepatitis and have an increased risk of progression to cirrhosis and HCC than those with MASLD alone.[154] MASLD is characterised by chronic low-grade inflammation, primarily driven by the activation of KCs and elevated levels of pro-inflammatory cytokines such as IL-6 and TNF-α. In contrast, MetALD exhibits a more pronounced inflammatory response, encompassing not only the chronic inflammation associated with MASLD but also acute alcohol-induced inflammation.

The involvement of immune cells

Inflammation in MetALD is characterised by infiltration of neutrophils and macrophages, as observed in animal models.[155] Cytokines and chemokines, such as CXCL1 and IL-8, promote neutrophil infiltration, leading to increased intrahepatic neutrophil levels in ALD. Binge alcohol consumption significantly elevates hepatic and circulating neutrophil levels in HFD-fed mice, ethanol-fed mice, and patients with alcohol use disorders.[156–159] Neutrophilic ROS, regulated by NCF1 (neutrophil cytosolic factor 1), exacerbate liver inflammation and injury by disrupting AMP-activated protein kinase and microRNA-223.[160] Notably, microRNA-223 regulates neutrophil infiltration and attenuates ethanol-induced liver injury by suppressing IL-6 and NCF1 expression. Recent RNA sequencing studies have revealed increased IL-8^{+} neutrophils in alcohol-associated hepatitis, with neutrophil infiltration playing a critical role in the progression from alcohol-associated cirrhosis to severe alcohol-associated hepatitis.[161] In addition, alcohol induces NET formation, which contributes to liver damage. NET release by high-density neutrophils generates low-density neutrophils that reside in the liver and evade clearance by macrophages.[162] All of these mechanisms mediated by neutrophils in ALD likely also contribute to the pathogenesis of MetALD.

The origin and fate of hepatic macrophage subpopulations have been a major area of focus, as these cells are integral to liver homeostasis and injury responses, offering potential insights for therapeutic strategies. For instance, macrophage subpopulations such as LAMs influence lipid metabolism and immune regulation. To further investigate the dynamics of different macrophage subpopulations in MetALD, Sasaki *et al.*

analysed the western diet with alcohol animal model and conducted chronic KC depletion experiments.[163] Their findings indicated that both scar-associated macrophages and LAM-like KC populations originate from circulating monocytes rather than embryo-derived resident KCs, suggesting that LAM-like KCs represent a subset of moKCs. However, it remains unclear whether alcohol-associated hepatotoxicity affects the persistence of moKCs. In the western diet with alcohol model, chronic KC depletion led to increased expression of inflammatory mediators and exacerbated liver fibrosis in mice. However, the precise mechanisms by which KCs exert their protective effects remain unclear.

Gut-liver axis in MetALD pathogenesis

Microbial dysbiosis, intestinal barrier dysfunction, and intestinal immune cells play crucial roles in driving liver inflammation in MetALD. Dysregulation of the gut microbiota is a key contributor to MetALD pathogenesis, frequently resulting from high-fat or high-carbohydrate diets and/or alcohol intake, which disrupts intestinal barrier integrity, leading to endotoxemia.[164] Alcohol consumption further alters the composition of the gut microbiota by promoting the proliferation of pro-inflammatory bacteria while depleting beneficial commensal species. This dysbiosis increases bacterial endotoxin production, which activates hepatic KCs and initiates an inflammatory cascade via the TLR4 signalling pathway, thereby exacerbating hepatic inflammation and fibrosis and accelerating disease progression.

Both MASLD and MetALD are influenced by intestinal barrier dysfunction and gut microbiota dysbiosis. In MASLD, diet-induced gut dysbiosis primarily increases intestinal permeability through metabolic endotoxemia. However, alcohol exacerbates intestinal barrier dysfunction more severely than dietary factors through multiple mechanisms. Specifically, alcohol uniquely disrupts tight junction proteins, leading to intestinal epithelial damage and increases permeability, which facilitates the translocation of endotoxins, such as LPS, into the portal circulation, thereby triggering hepatic inflammation.[165] Furthermore, alcohol-induced reduction of intestinal immune cells compromises intestinal immune function, further weakening the intestinal barrier.[166]

The critical role of adipose tissue in MetALD

Adipose tissue serves not only as a direct target of alcohol but also as a metabolic organ involved in the processing of alcohol metabolites, such as acetaldehyde. Alcohol consumption significantly alters the storage and secretory functions of adipocytes, exacerbating liver inflammation through multiple mechanisms.[167]

First, alcohol modifies the secretory profile of adipokines. These adipokines include pro-inflammatory cytokines (*e.g.* TNF-α, IL-6) and chemokines (*e.g.* CCL2), which affect liver function through paracrine signalling. Elevated levels of TNF-α and IL-6 enhance the recruitment and activation of immune cells in the liver. Additionally, alcohol increases oxidative stress within adipocytes, leading to the excessive generation of ROS. These ROS not only cause structural damage to adipocytes but also upregulate pro-inflammatory cytokine expression, further amplifying inflammatory responses. Moreover, alcohol-induced adipose tissue dysfunction increases the production of FFAs, which enter the liver through the bloodstream, where they promote lipid accumulation in hepatocytes. This accumulation results in lipotoxicity, triggering inflammatory responses and exacerbating liver injury. By altering adipokine secretion, increasing oxidative stress, and disrupting lipid metabolism, adipose tissue significantly contributes to the progression of hepatic inflammation and fibrosis in the context of alcohol consumption. These mechanisms highlight the complex interplay between adipose tissue and liver inflammation in the pathogenesis of MetALD.

Unique therapeutic challenges in MetALD

Given the complexity of MetALD, which involves both metabolic dysfunction and the direct hepatotoxic effects of alcohol, effective therapeutic strategies should target the multiple mechanisms driving its progression. However, despite over 1,200 clinical trials being conducted for steatotic liver disease, most have focused on MASLD, with limited attention paid to MetALD, because patients with significant alcohol intake have traditionally been excluded from therapeutic studies. Although an optimal approach to MetALD treatment would involve identifying drugs effective against MASLD while also promoting alcohol abstinence, the safety and interaction of such treatments with alcohol use disorders remain largely unclear.

FXR agonists

Studies have shown that activating FXR can alleviate liver damage in ALD mouse models by regulating lipid homeostasis, reducing oxidative stress, and decreasing inflammation. For example, the use of FXR agonists can improve lipid homeostasis, alleviate cholestasis, and reduce cellular senescence and inflammation in ALD.[168] However, all current insights into FXR activation in ALD are based on preclinical research.

GLP-1R agonists

Preclinical studies indicate that PPARα/γ activation reduces ethanol intake in mouse models of alcohol dependence, suggesting the potential for repurposing PPARα/γ agonists for the treatment of alcohol use disorder.[169] Similarly, with the potential to attenuate the reinforcing effects of alcohol, GLP-1R agonists may offer therapeutic benefits for MetALD, although their influence on alcohol consumption has not yet been confirmed in human studies.[170]

FGF21 agonists

In both patients with alcohol use disorder and corresponding animal models, alcohol consumption is associated with increased levels of circulating FGF21.[171] However, FGF21 itself reduced alcohol consumption through its action on the amygdala-striatal circuit.[172] These findings suggest that increasing FGF21 activity may be beneficial in suppressing alcohol use. Further studies are necessary to evaluate the effects of alcohol cessation on MetALD and to determine the therapeutic potential of FGF21 agonists.

Targeting the gut-liver axis

Targeting intestinal barrier dysfunction through the use of probiotics, prebiotics, or other microbiome-targeted therapies may help restore barrier integrity and reduce endotoxemia.[173]

Additionally, microbiome-targeted treatments, such as faecal microbiota transplantation (FMT), could support microbiome restoration and attenuate hepatic inflammatory signalling, potentially slowing MetALD progression. Although FMT has not yet been investigated specifically for MetALD, studies in patients with severe alcohol-associated hepatitis have demonstrated promising results, including significant reductions in alcohol cravings and alcohol-related adverse events compared to placebo-treated patients.[174] While findings from these studies on alcohol-associated hepatitis cannot be directly applied to MetALD, the potential impact on alcohol consumption, intestinal barrier function, and metabolic status highlights FMT as an important area of ongoing research for MetALD treatment.

De novo *lipogenesis inhibitors*

De novo lipogenesis inhibitors have the potential to mitigate steatosis caused by alcohol consumption. However, their effects on alcohol metabolism remain uncertain, and it is unclear whether these inhibitors would exacerbate or alleviate oxidative stress induced by alcohol metabolism. While their role in MetALD treatment may initially be limited, *de novo* lipogenesis inhibitors could become more effective in patients who have experienced substantial remission.

Conclusions and perspectives

Inflammation plays a central role in driving the progression of steatosis to steatohepatitis and eventually to HCC. Although recent studies have significantly expanded our understanding of the inflammatory mechanisms underlying steatotic liver disease and HCC pathogenesis, which encompasses diverse immune cells, cytokines, chemokines, and interorgan interactions, the complex and dynamic nature of the immune network has left many questions unresolved. Notably, although advances in analytical techniques have identified new immune cell subsets, such as LAMs, their functions remain largely uncharacterised. Despite extensive efforts to target inflammation in steatotic liver disease, few agents have shown clinical efficacy.

Steatotic liver disease arises from two primary aetiologies: alcohol consumption and metabolic dysfunction. Although these conditions share similar phenotypic characteristics, their clinical progression varies, necessitating a distinct understanding of the inflammatory mechanisms underlying each aetiology. In addition, the immunosuppressive microenvironment in MASLD and MASH-related HCC is not completely understood, and the interplay between alcohol and metabolic dysfunction in MetALD has yet to be clearly understood. Advancing our understanding of inflammation in this context will be critical for improving clinical investigations and therapeutic strategies. For instance, elucidating inflammation-related pathways may facilitate the identification of specific biomarkers that accurately reflect disease severity and progression. Such biomarkers could enable the differentiation between benign steatosis and advanced stages of MASLD, allowing for earlier and more precise diagnoses. Moreover, a comprehensive understanding of inflammation will support the design of more targeted clinical trials by aiding in the selection of patient subpopulations based on inflammatory profiles, thereby enhancing trial success rates and expediting the approval of novel therapies. Further research into the inflammatory mechanisms of steatotic liver disease holds the potential to identify new therapeutic targets, ultimately leading to more effective treatment strategies.

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Abbreviations

ALD, alcohol-associated liver disease; BAs, bile acids; CCR, C–C chemokine receptor; CXCR, C-X-C chemokine receptor; DAMP, damage-associated molecular patterns; DCs, dendritic cells; cDC, conventional dendritic cell; ER, endoplasmic reticulum; FFAs, free fatty acids; FGF, fibroblast growth factor; FMT, faecal microbiota transplantation; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; HCC, hepatocellular carcinoma; HFD, high-fat diet; HSCs, hepatic stellate cells; IL-, interleukin-; ILCs, innate lymphoid cells; ILTs, innate-like T cells; iNKT, invariant NK T; KCs, Kupffer cells; LAMs, lipid-associated macrophages; LPS, lipopolysaccharide; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MDSCs, myeloid-derived suppressor cells; MetALD, metabolic dysfunction and alcohol-related liver disease; moKCs, monocyte-derived KCs; moMFs, monocyte-derived macrophages; NET, neutrophil extracellular traps; NRG4, neuregulin 4; OCA, obeticholic acid; PD-1, programmed death-1; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; SFAs, saturated fatty acids; TAMs, tumour-associated macrophages; TGF-β, transforming growth factor-β; Th, T helper; THR-β, thyroid hormone receptor-β; TLR, Toll-like receptor; TNF-α, tumour necrosis factor-α; Tregs, regulatory T cells.

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Conflict of interest

The authors of this study declare that they do not have any conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Y.K., Y.P., H.R., and T.Y. wrote the manuscript. B.G. and S.H. wrote and edited the manuscript. All authors contributed to the article and approved the submitted version.

Supplementary data

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