

## Macrophages in metabolic associated fatty liver disease

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### Abstract

Metabolic associated fatty liver disease (MAFLD), formerly named non-alcoholic fatty liver disease is the most common liver disorder in many countries. The inflammatory subtype termed steatohepatitis is a driver of disease progression to cirrhosis, hepatocellular carcinoma, liver transplantation, and death, but also to extrahepatic complications including cardiovascular disease, diabetes and chronic kidney disease. The plasticity of macrophages in response to various environmental cues and the fact that they can orchestrate cross talk between different cellular players during disease development and progression render them an ideal target for drug development. This report reviews recent advances in our understanding of macrophage biology during the entire spectrum of MAFLD including steatosis, inflammation, fibrosis, and hepatocellular carcinoma, as well as for the extra-hepatic manifestations of MAFLD. We discuss the underlying molecular mechanisms of macrophage activation and polarization as well as cross talk with other cell types such as hepatocytes, hepatic stellate cells, and adipose tissue. We conclude with a discussion on the potential translational implications and challenges for macrophage based therapeutics for MAFLD.

**Key words:** Metabolic associated fatty liver disease; Macrophages; Inflammation; Fibrosis; Hepatic stellate cells

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**Core tip:** In this work, we review the recent advances in our understanding of macrophage biology during the entire spectrum of metabolic associated fatty liver disease (MAFLD) including steatosis, inflammation, fibrosis, and hepatocellular carcinoma, as well as for the extra-hepatic manifestations of MAFLD. We discuss the underlying molecular mechanisms of macrophage activation and polarization as well as cross talk with other cell types such as hepatocytes, hepatic stellate cells and adipose tissue. We conclude with a discussion on the potential translational implications and challenges for macrophage based therapeutics for MAFLD.

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## INTRODUCTION

Metabolic associated fatty liver disease (MAFLD), formerly named non-alcoholic fatty liver disease has now reached an “alert” level, an outcome of its high prevalence and its clinical and economic burden. It is estimated that nearly 1 billion people are afflicted globally<sup>[1-3]</sup>, while projections suggest that the incidence of MAFLD and MAFLD-related complications will continue to burgeon over the next few decades<sup>[4]</sup>. By current indications, MAFLD is on trajectory to become the primary cause of hepatocellular carcinoma (HCC) and the primary indication for liver transplantation<sup>[5,6]</sup>. Of most concern, around 20 million people who have MAFLD are expected to die of their liver disease. MAFLD not only increases the risk of liver failure and HCC, but also increase the risk for extra-hepatic complications such as type 2 diabetes, cardiovascular disease, chronic kidney disease, osteoporosis, and some type of cancers. The estimated annual medical costs directly attributable to MAFLD is about \$100 billion in the United States and €35 billion in four large European countries (Italy, France, Germany and The United Kingdom)<sup>[7]</sup>.

The pathogenesis of MAFLD suggests that it is a heterogeneous disease with a variable clinical presentation shaped by interactions between gene and environmental cues<sup>[8,9]</sup>. In turn, the clinical presentation is affected by biological and chronological age<sup>[10]</sup>. Though MAFLD is classically linked to other metabolic dysfunction and disease such as diabetes and obesity with a shared genetic basis between the conditions<sup>[11]</sup>, it is now recognised that a significant proportion of patients are non-obese<sup>[1]</sup>. The spectrum of disease varies widely ranging from simple steatosis to the presence of inflammation, through to fibrosis, cirrhosis and HCC. Only a proportion (5%-10%) of patients with MAFLD will develop the more severe subtype of steatohepatitis, and some of these will progress to advanced liver fibrosis or cirrhosis, the leading cause of liver related morbidity, and mortality<sup>[12]</sup>. While HCC typically develops in the context of cirrhosis, it is increasingly described in patients even in its absence. Hence, the transition from steatosis to steatohepatitis represents a pivotal checkpoint in the natural history of patients with the disease. The current view is that innate immune mechanisms are central to the transition to hepatic inflammation<sup>[13]</sup> with macrophages playing a critical role. In this review, we provide a detailed overview on current knowledge on the role of macrophages for liver immune homeostasis and steatohepatitis development and the translational implications and challenges arising from this knowledge.

## HEPATIC MACROPHAGES

Hepatic macrophages consist of different cell populations including resident macrophages (aka Kupffer cells) which originate from the yolk sac and function as the dominant liver phagocyte. In addition, bone marrow derived monocytes in the circulation can infiltrate the liver<sup>[14]</sup>.

The liver has the largest proportion of tissue macrophages among solid organs and it is estimated that for every 100 hepatocytes in a healthy rodent, there are between 20-40 macrophages<sup>[15]</sup>. This emphasizes the critical role of liver macrophages in maintaining liver homeostasis<sup>[16]</sup>, but also indicates the high levels of heterogeneity of this cell population that must exist to enable homeostasis maintenance. Two recent studies employed single cell RNA sequencing to de-convolute hepatic macrophage heterogeneity. In these studies, distinct hepatic macrophage populations with inflammatory and non-inflammatory/immunoregulatory functions were demonstrated<sup>[17]</sup>. The second study demonstrated that myeloid cells in liver and bone marrow acquire a functionally distinct inflammatory phenotype in diet induced mouse models of steatohepatitis<sup>[18]</sup>.

Physiologically, hepatic immune homeostasis is controlled by sinusoidal endothelial cells with liver macrophages part of the liver reticulo-endothelial system<sup>[19]</sup>. A recent report suggests that liver macrophages compromise two separate and non-overlapping niches mediating immunosurveillance and that the hepatic

capsule has a cellular network of resident macrophages phenotypically distinct from KCs. These cells sense peritoneal bacteria and restricts hepatic dissemination of these bacteria by promoting neutrophil recruitment to the capsule<sup>[20]</sup>. This system creates a dynamic and complex network which therefore constitutes the first line of defence against invading pathogens with contribution of other immune cells such as neutrophils<sup>[16]</sup>. At the same time, the upkeep of tissue homeostasis is monitored by the reticuloendothelial system through the production of immunoregulatory cytokines such as interleukin-10 and programmed cell death 1 ligand 1<sup>[21]</sup>. Their function includes scavenging bacteria and bacteria-associated products which end up in the liver from the intestine through the portal vein<sup>[22]</sup>. However, alterations in this fine-tuned system can lead to different pathological disorders and is strongly implicated in MAFLD development.

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## MACROPHAGE POLARIZATION

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Macrophage polarization is the process whereby macrophages differentiate into sub-phenotypes with specific biological functions in response to signals from their microenvironment including cytokines, growth factors, fatty acids, prostaglandins and pathogen-derived molecules. A simplified classification is the M1 and M2 based activation state<sup>[23,24]</sup>. M1 macrophages are pro-inflammatory and antimicrobial and initiate inflammatory processes by expressing high levels of proinflammatory cytokines and producing high amounts of reactive oxygen and nitrogen species<sup>[25]</sup>. In contrast, M2 macrophages have anti-inflammatory and reparative functions with high expression of different chemokines compared with M1 macrophages<sup>[24,25]</sup>. However, the true complexity of macrophage phenotypes and their regulation is greater than described above and is context dependent and dynamic<sup>[26]</sup>. Difficulties in interpreting many published reports results from insufficient characterization of macrophage polarization and function<sup>[14]</sup>.

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## MACROPHAGES AND THEIR ROLES IN MAFLD

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### ***Macrophages, steatosis development, and the transition to steatohepatitis***

Macrophages are highly versatile, while extensive experimental and clinical data indicates that they play a central role in MAFLD development with pro-inflammatory macrophages determining disease severity<sup>[14]</sup>. In human MAFLD, portal macrophage infiltration is observed at an early stage before inflammation is evident and is associated with progressive disease<sup>[27]</sup>. Another study of young adult Koreans showed an increase in the numbers of CD68<sup>+</sup> Kupffer cells in biopsy samples from patients with steatohepatitis compared to those with steatosis<sup>[28]</sup>. Similarly, an increase of activated macrophages was found in children with MAFLD and these were located in the vicinity of damaged hepatocytes<sup>[29]</sup>.

Additional evidence for a central role for macrophages in steatohepatitis comes from experimental models. In dietary mouse models, an increase in hepatic macrophages that produce pro-inflammatory cytokines was observed in high-fat diet (HFD) and methionine-choline-deficient (MCD) diet fed mice<sup>[30,31]</sup>. Moreover, the production of these inflammatory mediators was increased after 4 wk in mice fed a MCD diet and decreased subsequently, suggesting a determinant role in the transition to steatohepatitis<sup>[32]</sup>. In addition, immune responses are innately different between mouse strains; T helper 1 cell and M1 responses are observed in C57BL/6 mice whereas T helper 2 cell and M2 response are observed in BALB/c mice<sup>[33]</sup>. Feeding these two strains an MCD diet showed that steatosis and hepatic inflammation was more induced in M1-prone C57BL/6 mice compared with the M2 prone BALB/c strain<sup>[34]</sup>. Furthermore, the use of clodronate liposomes or gadolinium chloride to deplete macrophages protected mice from steatosis development<sup>[35]</sup>.

Pro-inflammatory macrophages have also been found to induce hepatic insulin resistance and decrease hepatocyte responsiveness to insulin by attenuating phosphorylation of the insulin receptor substrate 1 in hepatocytes<sup>[36]</sup>. Thus, silencing of *NF-κB* specifically in Kupffer cells improves insulin sensitivity and decreases cytokine secretion in a HFD-fed model further suggesting a crucial role for them in hepatic insulin resistance<sup>[37]</sup>. Another report found that HFD-fed mice injected with clodronate to deplete Kupffer cells had decreased steatosis and steatohepatitis *via* reducing interleukin-1β-dependent suppression of peroxisome proliferator-activated receptor-α (PPARα)<sup>[38]</sup>. The latter is suggested to have an anti-inflammatory role in liver and adipose tissue<sup>[39]</sup>. Along the same line, depletion of Kupffer cells leads to reduction of inflammatory cytokine expression and decreases inflammation and liver

cell death<sup>[40]</sup>. Another suggested mechanism is of p38 mitogen-activated protein kinases being upregulated in the liver of patients with MAFLD in multiple diet induced steatohepatitis mouse models. Macrophage p38 induces M1 polarization and pro-inflammatory cytokine secretion promoting the progression to steatohepatitis<sup>[41]</sup>.

### **Macrophages and liver fibrosis**

In virtually all chronic liver diseases, there is no fibrosis without preceding or concomitant inflammation. Liver macrophages play a pivotal role in fibrosis progression with these cells and hepatic stellate cells (HSCs, the major producer of extracellular matrix) exhibiting bidirectional signalling<sup>[42]</sup>. Thus, chemokines/cytokines from HSCs augment macrophage infiltration, while macrophages amplify inflammation, contribute to maintain the fibrogenic phenotype and promotes HSC survival. Macrophages also play a dominant role in fibrosis resolution. Alternatively activated M2 macrophages correlate with hepatic injury in MAFLD<sup>[31]</sup> orchestrating a fibrosis response favouring liver remodelling and tissue repair by producing transforming growth factor- $\beta$  and platelet-derived growth factor among other proteins<sup>[43]</sup>.

Distinct monocytes/macrophage populations can be found in human and mouse liver based on levels of Ly-6C (Gr1) or CD14/CD16 expression, in murine and humans respectively. In humans it includes “classical” CD14<sup>++</sup>CD16<sup>-</sup> and “non-classical” CD14<sup>+</sup>CD16<sup>+</sup> monocytes/macrophages as well as CD16<sup>++</sup> cells. Notably, fibrosis is associated with preferential enrichment of CD14<sup>+</sup>CD16<sup>+</sup> cells or its functional counterpart Ly-6C<sup>hi</sup> in mouse<sup>[44,45]</sup>. These cells activate HSCs *in vitro*, partially dependent on transforming growth factor (TGF)- $\beta$  release<sup>[44,45]</sup>. Conversely, the production of soluble mediators such as CC-chemokine ligand 2 (also known as MCP1) and macrophage colony-stimulating factor by activated HSCs augments inflammatory cell infiltration to initiate and maintain myofibroblast activation<sup>[46]</sup>. Ly-6C<sup>lo</sup> cells have been identified as a feature of “restorative” hepatic macrophages in mice<sup>[47]</sup> but the exact counterpart of these in humans remains to be clarified. In mouse models, autophagy gene *Atg5* in the myeloid lineage *Atg5*(fl/fl) *LysM-Cre* knockout mice have demonstrated that macrophage autophagy attenuates liver fibrosis<sup>[48]</sup>. Additionally, immune cell subset differentiation can perpetuate or restrict hepatic injury<sup>[49]</sup>.

In sum, at different stages of hepatic injury, both resident Kupffer cells and freshly recruited monocyte-derived macrophages play critical roles in the regulation of inflammation, fibrosis and fibrolysis<sup>[49]</sup>.

### **Macrophages and HCC**

MAFLD can increase the risk of HCC even in the absence of cirrhosis<sup>[50]</sup>. Tumor associated macrophages secrete inflammatory cytokines such as tumour necrosis factor- $\alpha$  and growth factors such as vascular endothelial growth factor and TGF- $\beta$  that are involved in angiogenesis and contribute to tumor development, progression, and metastasis<sup>[51]</sup>. Toll like receptor (TLR) 4 but not TLR2 on macrophages has also been demonstrated to contribute to steatohepatitis-related HCC in mice by inducing proinflammatory cytokines and the proliferation of HCC and cancer progenitor cells<sup>[52]</sup>. Another mechanistic study suggests that obesity-associated oxidative stress increases STAT-1 and STAT-3 signaling which can independently contribute to the pathogenesis of steatohepatitis, fibrosis, and HCC in mouse models<sup>[53]</sup>.

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## **MACROPHAGES AND MAFLD EXTRA-HEPATIC MANIFESTATIONS**

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The consequences and complications of MAFLD are not limited to liver, but also extend to include various extra-hepatic organ involvement including type 2 diabetes mellitus, chronic kidney disease, osteoporosis, hypothyroidism, some type of cancers, and cardiovascular disease<sup>[54]</sup>. The mechanisms that contribute to this heightened risk for cardiovascular disease and type 2 diabetes mellitus risk are poorly understood.

Disordered myelopoiesis and macrophage-mediated inflammation was recently suggested as a plausible overarching mechanism linking MAFLD to cardiovascular diseases<sup>[55]</sup>. Soluble CD163, a macrophage activation marker correlates with liver injury<sup>[56]</sup> with similar finding reported for CVD risk<sup>[57]</sup>. As discussed above, apart from their central role in progression to steatohepatitis and fibrosis, macrophages are known to enter to plaques and promote lesion progression, instability and rupture<sup>[58]</sup>.

## FACTORS REGULATING MACROPHAGE PHENOTYPE AND PLORAIZATION IN MAFLD

### **Dietary factors**

Nutrition and the intracellular metabolism of macrophages are a key regulator of their function and can determine the skew of macrophages towards a pro or anti-inflammatory phenotype<sup>[59]</sup>. For example, dietary cholesterol differentially shapes the transcriptome of Kupffer cells and infiltrating macrophages during steatohepatitis progression towards a pro-inflammatory phenotype<sup>[60]</sup>. Similarly, a HFD induces macrophage polarization and aggravates the liver inflammatory microenvironment and cancer progression in a zebrafish model of MAFLD-associated HCC; this effect was reversed by metformin<sup>[61]</sup>. Conversely, exercise training and weight loss suppress macrophage activation as assessed by soluble CD163 (sCD163)<sup>[62,63]</sup>. Similarly, a reduction in sCD163 was noticed following bariatric surgery which was accompanied by improvements in insulin sensitivity and liver enzymes<sup>[64]</sup>. Functionally, endolysosomal lipid trapping and accumulation in Kupffer cells in response to high fat diet feeding upregulates hepatic inflammatory gene expression<sup>[65,66]</sup> while fatty acids can increase mitochondrial DNA release causing activation of NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasomes in Kupffer cells<sup>[67]</sup>. In contrast, vitamin D receptor activation in hepatic macrophages improves insulin resistance, steatosis and hepatic inflammation through the induction of an anti-inflammatory phenotype<sup>[68]</sup>.

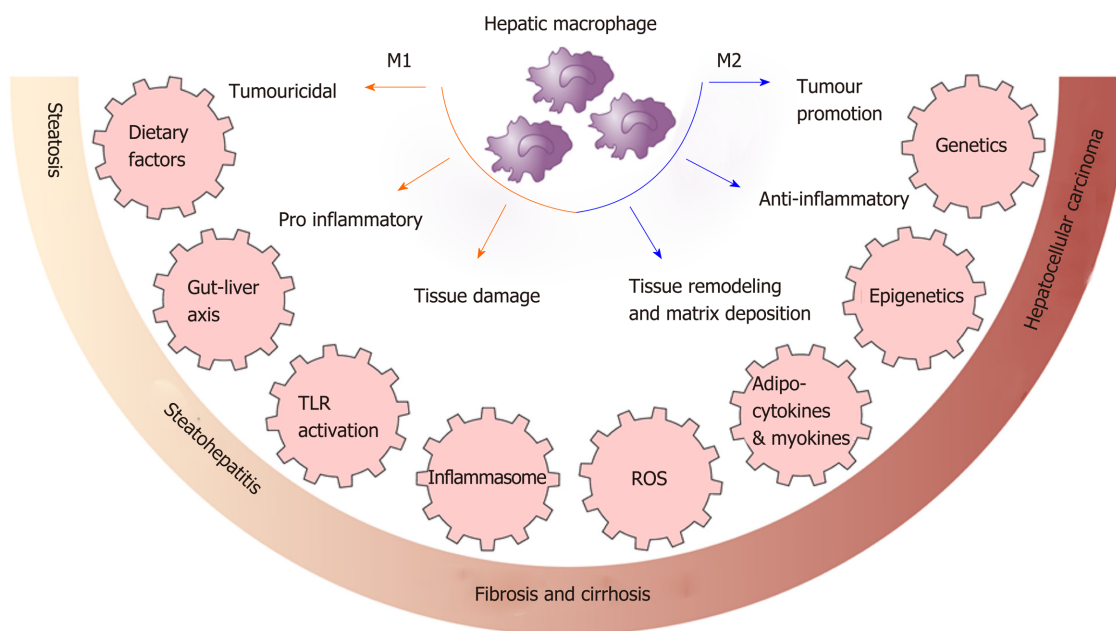
Hematopoiesis in bone marrow is influenced by environmental cues including diet. Myelopoiesis is tightly regulated in bone marrow<sup>[69]</sup>, governing the generation of mature cells *via* sequential progression from HSCs to differentiated cells including monocytes and macrophages that share a distinct committed progenitor<sup>[70,71]</sup>. Dysregulation of hematopoiesis switches the protective response to pro-inflammatory myelopoiesis in the marrow and governs ongoing and future inflammatory responses<sup>[72-74]</sup>. A recent study showed that bone marrow derived macrophages from western diet fed mice have an inflammatory activation profile compared to those from normal chow fed mice<sup>[48]</sup>.

Thus, dietary factors play a role in determining macrophage polarisation and activation as well as in shaping myelopoiesis. Macrophage polarisation and activation is shown in [Figure 1](#).

### **The Gut–liver axis**

Dysbiosis of the gut microbiota is a factor contributing to the development and progression of fatty liver disease<sup>[75]</sup>. Dysbiosis affects hepatic macrophage activation and polarization through multiple potential mechanisms. For example, the gut microbiome plays a central regulatory role in host metabolism whereby alterations in the metabolic outputs of intestinal microbiota affect macrophage polarization<sup>[75]</sup>. A recent study using metabolomics analysis of cecal and fecal material from germ-free and conventionally raised HFD fed mice identified a gut microbiota-derived metabolite indole-3-acetate that directly modulates inflammatory responses in macrophages and dampens the release of pro-inflammatory cytokines<sup>[76]</sup>. Mechanistically, these effects were mediated through the aryl-hydrocarbon receptor, a transcription factor that regulates responses to multiple environmental signals including dietary factors<sup>[76]</sup>. In the same vein, ARNT mRNA expression is downregulated in liver tissues from MAFLD patients, while deletion of ARNT in mouse myeloid cells leads to steatohepatitis<sup>[77]</sup>. Similarly, the dysregulation of gut microbiota of infants of obese mothers leads to impaired macrophage function including cytokine production, phagocytosis and adaptation to various stimuli that ultimately increases susceptibility to MAFLD<sup>[78,79]</sup>.

Another mechanism exists whereby alterations in the intestinal permeability in patients and murine models of MAFLD that is mediated by a western diet, leads to increases in the circulating levels of bacterial products including lipopolysaccharide (LPS). This leads to activation of TLRs, a sensor for these products<sup>[80]</sup> and results in macrophage activation and the initiation of injury<sup>[81-85]</sup>. Serum LPS and hepatic TLR4<sup>+</sup> macrophages are higher in steatohepatitis patients compared to those with MAFLD or control subjects<sup>[86]</sup>. Similarly hepatic TLR 2, TLR4 and TLR9 expression was upregulated in human and murine steatohepatitis but not in simple steatosis; expression was localized to inflammatory cells, particularly macrophages<sup>[87]</sup>. Finally, Tlr4 and Tlr9 KO mice are protected from steatohepatitis induced by different diet models of MAFLD such as MCD feeding or a cholesterol rich diet<sup>[88,89]</sup>. Notably, the TLR effects also involves interaction and activation with other intersecting pathways with a role in inflammation. In a recent study, LPS treatment induced the accumulation of yes-associated protein (YAP) in Kupffer cells, a transcription



**Figure 1 Macrophage polarisation and activation.** Macrophages polarize to sub-phenotypes with specific biological functions in response to signals from their microenvironment. These include signals from adipocytokines and myokines, the gut liver axis and toll-like receptor activation, damaged hepatocytes, reactive oxygen species, genetic and epigenetic factors. The process of macrophage activation is a critical determinant of disease progression and is a target for potential treatment. ROS: Reactive oxygen species; TLR: Toll-like receptor.

coactivator that plays a role in the Hippo-YAP pathway and is implicated in the immune response<sup>[90]</sup>. YAP accumulation in Kupffer cells in steatohepatitis enhances the production of pro-inflammatory cytokines<sup>[90]</sup>. Furthermore, the elevated LPS in MAFLD<sup>[84,85]</sup> provides a critical hit for sustained inflammasome activation in macrophages<sup>[91]</sup>.

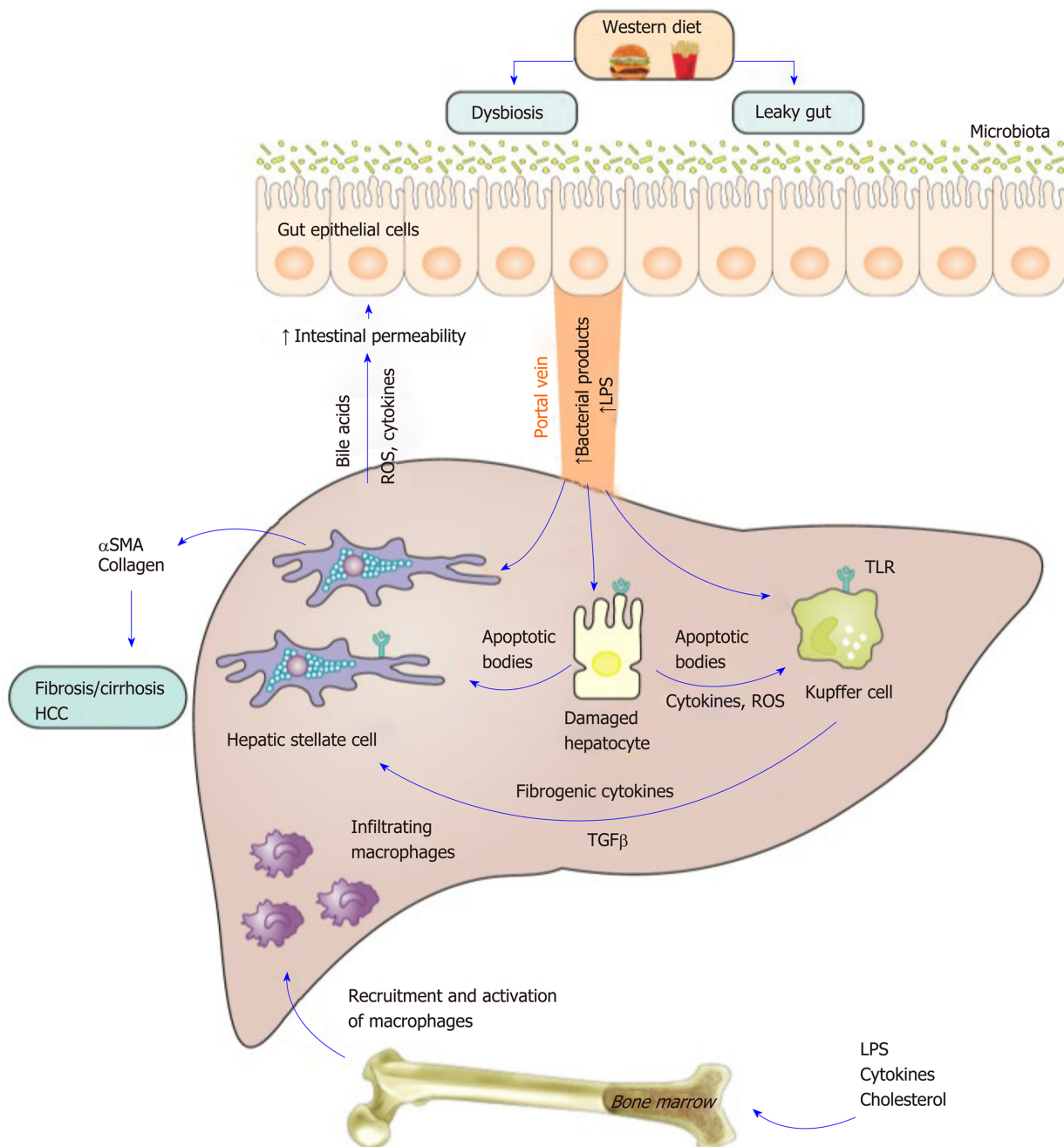
TLR4 stimulation also induces alterations in lipid homeostasis<sup>[92]</sup> and macrophage activation as assessed by sCD163 as was found in a small trial that included 8 healthy male subjects<sup>[93]</sup>. In that study, sCD163 correlated with accelerated lipolysis following LPS exposure and enhanced mitochondrial reactive oxygen species (ROS) generation, a trigger for inflammasome activation<sup>[94]</sup>.

Collectively, gut dysbiosis is implicated in macrophage activation and hepatic inflammation through multiple mechanisms including by alterations in the metabolic outputs of microbiota, increased bacterial products generation and the activation of TLRs and inflammasomes. The gut liver axis in metabolic associated fatty liver disease is shown in **Figure 2**.

### **Adipocytokines and myokines**

Both adipocytokines and myokines play an important regulatory role in macrophage activation and polarisation. The anti-inflammatory effects of adipocyte-derived adiponectin can partially be attributed to promoting the polarization of macrophages toward an anti-inflammatory phenotype<sup>[95]</sup> as well as promoting macrophage tolerance to pro-inflammatory stimuli<sup>[96]</sup>. Adiponectin KO mice are more prone to steatohepatitis, while adiponectin administration attenuates steatohepatitis progression by reducing macrophage infiltration and skewing polarization towards an anti-inflammatory phenotype<sup>[97]</sup>. Levels of leptin are increased in MAFLD and this regulates macrophage phenotype including Kupffer cell activation, inflammatory phenotype and sensitivity to LPS-induced induced inflammatory cytokine secretion and acquisition of a fibrogenic phenotype<sup>[98-100]</sup>. A previous study showed that Kupffer cells likely mediate leptin-induced liver fibrosis effects by inducing the upregulation of fibrogenic gene expression such as that of TGF $\beta$ 1 and connective tissue growth factor<sup>[100]</sup>.

Levels of fibronectin type III domain-containing 5 (FNDC5) a myokine with favourable metabolic effects is decreased in MAFLD and correlates with the severity of hepatic steatosis<sup>[101]</sup>. FNDC5 attenuates adipose tissue insulin resistance and inflammation *via* AMP-activated protein kinase-induced macrophage polarization in a high fat diet mice model<sup>[102]</sup>. Another member of the fibronectin type III domain family of proteins is FNDC4 a secreted factor with a high homology to FNDC5. This was demonstrated to have anti-inflammatory effects on macrophages by reducing



**Figure 2 The gut liver axis in metabolic associated fatty liver disease and the central role of macrophages.** A western diet alters gut permeability and causes dysbiosis. This increases hepatic exposure to lipopolysaccharide and bacterial products and leads to toll-like receptor activation in hepatocytes, hepatic stellate cells and macrophages; the latter are the main responsive cells. Hepatocyte injury leads to the generation of apoptotic bodies, reactive oxygen species and cytokines. Engulfment of apoptotic bodies by macrophages increases expression of death ligands such as tumor-necrosis-factor-related apoptosis-inducing ligand, Fas, and tumour necrosis factor- $\alpha$  leading to a feed-forward loop that promotes further hepatocyte apoptosis. Engulfment of apoptotic bodies by hepatic stellate cells promotes their activation and the secretion of transforming growth factor  $\beta$ 1 and extracellular matrix, promoting fibrosis and subsequently cirrhosis. Activated macrophages also lead to increased activation of stellate cells. Cholesterol, bacterial products and cytokines can stimulate myelopoiesis in bone marrow. Infiltrating monocytes lead to amplification of the inflammatory response. Increased bile acid and reactive oxygen species production by the injured liver also contributes to damage to gut epithelial cells and to detrimental alterations in microbiota setting up a vicious cycle of injury. LPS: Lipopolysaccharide; TLR: Toll-like receptor; TGF- $\beta$ : Transforming growth factor  $\beta$ ; HCC: Hepatocellular carcinoma.

proinflammatory chemokine expression and dampening macrophage activity<sup>[103]</sup>. The role of FNDC4 in MAFLD is unknown. In sum, adipocytokines and myokines represent another crucial regulator of macrophage biology in the context of metabolic disorders.

#### **Damaged hepatocytes and ROS and macrophage activation**

Damaged hepatocytes are a trigger for macrophage activation. Data from mice fed a HFD suggest that steatotic hepatocytes promote the release of pro-inflammatory cytokines by macrophages, indicating that hepatocyte damage elicits macrophage

activation<sup>[104]</sup>. In turn, apoptotic body engulfment by Kupffer cells is a potent trigger for inflammation and fibrosis and for activation of macrophages *via* pattern recognition receptors such as TLRs<sup>[105]</sup>. Trying to elucidate the link between damaged hepatocytes and macrophage activation and inflammation, a recent study has suggested that proapoptotic lipotoxic signaling by death receptor 5 (also known as tumor necrosis factor receptor superfamily member 10b) induces the release of extracellular vesicles from hepatocytes. These in turn activate macrophages and promotes an inflammatory phenotype<sup>[106]</sup>. Similarly, another study showed that hepatocytes release ceramide-enriched pro-inflammatory extracellular vesicles under lipotoxic conditions that promote macrophage recruitment to the liver<sup>[107]</sup>. Recent reports have also demonstrated increased expression of the G protein-coupled transmembrane receptor Smoothed and glioma-associated oncogene (Gli) transcription factors (components of the hedgehog signaling pathway) in primary hepatocytes from damaged livers<sup>[108]</sup>. Pharmacological and genetic liver specific inhibition of Smoothed prevented hepatic inflammation in MAFLD models through decreased macrophage recruitment and activation<sup>[109]</sup>.

ROS are another potential mechanism for macrophage activation. ROS impacts Kupffer cells both directly and indirectly. ROS prompts tumour necrosis factor- $\alpha$  generation in Kupffer cells and they can increase the susceptibility of these cells to endotoxin<sup>[110,111]</sup>.

### **Genetic variants that influence macrophage function and thereby liver inflammation**

There is strong evidence that MAFLD has high heritability with a shared genetic basis between MAFLD and other liver diseases as well as with other metabolic disorders<sup>[11]</sup>. The genetic basis of macrophage activation is still not known, however several genetic variants implicated in MAFLD have been demonstrated to regulate macrophage phenotype. For example, the interferon lambda 3/4 (*IFNL3/IFNL4*) genotype is strongly associated with hepatic inflammation and fibrosis in MAFLD as well as hepatitis C and B<sup>[112,113]</sup> and scores incorporating these variants with other clinical variables can predict liver fibrosis in patients<sup>[114]</sup>. A correlation between *IFNL3/IFNL4* genotype and hepatic macrophage infiltration as well as macrophage activation as assessed by the activation marker sCD163 has been reported<sup>[115-119]</sup>. Recently, increases in hepatic *IFNL3* expression in liver tissues from patients with MAFLD compared to controls was also reported<sup>[120]</sup>. *IFNL3* skews macrophages toward a proinflammatory phenotype orchestrating their interaction with other immune cells including T-cells to mediate hepatic inflammation<sup>[120]</sup>.

Another example is of variants in the Membrane Bound O-Acyltransferase Domain Containing 7 (*MBOAT7*) gene that encodes an acyltransferase enzyme and catalyses the transfer of an acyl-CoA to lysophosphatidylinositol. This regulates the availability of arachidonic acid for pro-inflammatory eicosanoids production<sup>[121-124]</sup>. A variant (rs641738) in the *MBOAT7* gene is associated with liver injury in MAFLD as well as in viral hepatitis<sup>[121-124]</sup>. *MBOAT7* is robustly expressed by inflammatory cells including macrophages and this variant associates with macrophage activation as assessed by sCD163; the detailed mechanisms for this association are unknown<sup>[121-124]</sup>. A recent study showed that *Mboat7* loss of function promotes the progression of MAFLD and hepatic inflammatory and fibrotic phenotypes in response to a high fat diet<sup>[125]</sup>.

Another example is a variant (rs4374383) in the MER Proto-Oncogene, Tyrosine Kinase (*MERTK*) gene, a member of the Tyro-Axl-MerTK family of receptor tyrosine kinases. By a genome-wide association study this polymorphism has been associated with fibrosis in patients with hepatitis C<sup>[126]</sup>. Similar findings were later observed in patients with MAFLD<sup>[127]</sup>. A recent study has shown that this variant regulates *MERTK* expression in circulating and hepatic macrophages and that total and myeloid specific *MERTK* deficiency decreased liver fibrosis in mice<sup>[128]</sup>.

### **Epigenetic regulation**

Epigenetic modifications include DNA methylation, histone modification and non-coding RNA<sup>[8]</sup>. Growing evidence suggests an important role for epigenetic mechanisms in the regulation of macrophage phenotype, polarization, inflammatory and profibrotic gene production. A recent work used reduced representation bisulfite sequencing in a mouse carbon tetrachloride (CCL4) fibrosis model and identified that hypermethylation of proline-serine-threonine-phosphatase-interacting protein2 links it to hepatic fibrosis<sup>[129]</sup>. In another study, the histone methyltransferase Suv39h2 was found to contribute to steatohepatitis in mouse models through suppression of PPAR $\gamma$ . This leads to macrophage polarisation towards a proinflammatory M1 over an anti-inflammatory M2 phenotype<sup>[130]</sup>. miRNAs are also implicated in macrophage activation and polarisation. For example, lipotoxic hepatocyte-derived exosomal miR-192-5p plays a pivotal role in the activation of proinflammatory macrophages and in disease progression of MAFLD *via* Rictor/Akt/FoxO1 signaling<sup>[131]</sup>.



## ADIPOSE TISSUE AND FATTY LIVER CROSS TALK: ROLE OF MACROPHAGES

A pivotal role for macrophages in the crosstalk between adipose tissue and liver in fatty liver disease has been suggested. Thus, adipose tissue insulin resistance and free fatty acid flux to liver activates hepatic macrophages in MAFLD independent of obesity and diabetes<sup>[132]</sup>. It has also been suggested that adipose tissue inflammation might precede hepatic inflammation since in high fat and cholesterol diet fed mice, the upregulation of genes associated with macrophage recruitment and inflammation occurred earlier in adipose tissue compared to the liver<sup>[133]</sup>. During obesity, both adipose tissue macrophage (ATM) numbers and activation are enhanced<sup>[134]</sup>. In humans, in a cohort of obese patients undergoing bariatric surgery, ATMs from patients with MAFLD and steatohepatitis produced higher levels of inflammatory cytokines compared to controls<sup>[135]</sup>. In animal models, ablation of these ATMs led to normalization of whole-body insulin sensitivity<sup>[136]</sup> while ATMs from obese visceral adipose tissue amplified hepatic inflammation through augmentation of hepatic macrophage infiltration<sup>[137]</sup>.

## TRANSLATIONAL IMPLICATIONS

Although MAFLD is a major clinical problem, to date there are no approved treatments. Recently, obeticholic acid was reported to improve MAFLD related fibrosis and will likely be the first drug to be approved for its treatment<sup>[138,139]</sup>. With multiple other investigational drugs in Phase 3 clinical trials, it can be expected that other drugs will follow and be approved. However, the efficacy of these drugs appears modest suggesting that more novel approaches to drug development are required<sup>[140]</sup>. Given the central role of macrophages in the transition to steatohepatitis and to fibrosis, macrophages might be a suitable target for therapy and as a biomarker of disease severity, as discussed below. The central role of macrophages is shown in [Figure 2](#).

### **Macrophage based diagnostic biomarkers**

Soluble CD163, a macrophage activation marker was reported to correlate with liver injury and demonstrated good predictive ability for advanced fibrosis ( $\geq$  F3) with an area under the receiver operating curve (AUROC) of 0.77 and 0.80 in two independent cohorts. This was further increased in combination with the MAFLD fibrosis score (AUROC of 0.83 for both cohorts)<sup>[56]</sup>. However, macrophage activation markers such as sCD163 and soluble mannose receptor demonstrated poor associations with liver histology in two cross-sectional paediatric MAFLD cohorts ( $n=155$  and  $36$ ) suggesting a differential role for macrophage activation in adult and paediatric disease or perhaps indicates that disease severity is different between adult and paediatric patients at least in the cohorts examined<sup>[141]</sup>.

A recent study also suggested that the circulating activity of adenosine deaminase (a macrophage-derived deaminase that converts adenosine or deoxyadenosine to inosine and derivatives) can predict MAFLD cirrhosis, advanced fibrosis ( $\geq$  F3), and significant fibrosis ( $\geq$  F2) with AUROCs of 0.94, 0.82, and 0.84, respectively<sup>[142]</sup>. However, the molecular mechanisms for this association are yet to be determined.

### **Macrophage based therapeutic targets**

Some macrophage-targeted therapies for liver diseases have been investigated in the clinic<sup>[143]</sup>. One of these is limiting monocyte and macrophage recruitment. Many of the pathways characterized in mice for monocyte recruitment are also strongly regulated in patients with liver diseases suggesting well conserved mechanisms across species. For instance, cenicriviroc, an oral dual inhibitor of the chemokine receptor C-C ligand/ receptor 2 and 5 pathway (inhibits hepatic monocyte infiltration)<sup>[144]</sup> was evaluated in a phase 2b clinical trial in patients with MAFLD and fibrosis. Early results suggest that patients receiving cenicriviroc oral therapy were twice as likely to have improvement of fibrosis (without worsening of steatohepatitis) after 1 year of follow up<sup>[141]</sup>. However, the differences did not appear to be significant by the second year of follow up.

Another approach for treatment is to promote anti-inflammatory macrophage polarization. The PPAR family that includes  $\alpha$ ,  $\beta/\delta$ , and  $\gamma$  is a member of the nuclear receptor superfamily and polarizes macrophages towards an anti-inflammatory state. This can explain at least partially their role in MAFLD<sup>[145,146]</sup>. For example, among modulators of the PPARs, PPAR $\gamma$  agonists such as pioglitazone have insulin sensitizing effects but also induces polarization of macrophages towards an anti-

inflammatory phenotype thereby improving hepatic steatosis<sup>[145,146]</sup>. Similarly, the PPAR $\alpha$ /PPAR $\gamma$  agonist saroglitazar reverses fibrosis in MAFLD<sup>[147]</sup> and elafibranor, an agonist of PPAR $\alpha$  and  $\delta$  attenuates hepatic inflammation without worsening fibrosis<sup>[148]</sup>. PPAR $\delta$  induces polarization of macrophages towards an anti-inflammatory M2 phenotype<sup>[145]</sup> while elafibranor decreases hepatic macrophage infiltration in animal models of MAFLD<sup>[149]</sup>.

An alternative approach is targeting activating signals for macrophages. For example, NLRP3 inflammasome pharmacological blockade using MCC950 attenuates hepatic inflammation and fibrosis in mouse models and reduces the numbers of macrophages in liver<sup>[150]</sup>. Currently, a clinical trial (NCT03676231) using an inflammasome inhibitor SGM-1019 is recruiting. TLR4 is a key regulator of MAFLD<sup>[151]</sup> however the results of a phase-2 study failed to discern a beneficial effect of JKB-121, a small molecule TLR-4 receptor antagonist in human MAFLD<sup>[152]</sup>.

The growing body of knowledge on immunometabolism and epigenetic regulation indicates that metabolic reprogramming and epigenetic regulation may be a target for regulating macrophage responses such as polarization and activation. Two recent reports demonstrate that digoxin improves steatohepatitis in mice models through regulation of the pyruvate kinase muscle isozyme M2-hypoxia-inducible factors axis in hepatocytes and macrophages<sup>[153,154]</sup>. Pyruvate kinase muscle isozyme M2 is a rate limiting glycolytic enzyme that catalyzes the final step in glycolysis<sup>[155]</sup> and promotes NLRP3 and AIM2 inflammasome activation in macrophages<sup>[156]</sup>.

In a recent study of mice fed a MCD diet, miR-141 and miR-200c deficiency attenuated hepatic steatosis and inflammation *via* multiple mechanisms including reprogramming of macrophages toward anti-inflammatory phenotype<sup>[157]</sup>. Although several epigenetic drugs are currently approved for treating different type of cancers, data are still limited on effects of these drugs on macrophage activation and polarisation. Histone deacetylase inhibition was demonstrated to improve post-myocardial infarction healing through modulating macrophage polarization<sup>[158]</sup>. Another study showed that targeting histone deacetylases in myeloid cells using CHR-4487 (ESM-HDAC528) a small molecule that can inhibits their inflammatory phenotype has a limited impact in atherosclerosis<sup>[159]</sup>; there is no data on MAFLD.

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## CHALLENGES AND OPEN QUESTIONS

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Although targeting macrophages is attractive, a major obstacle for the development of therapies is that of macrophage heterogeneity and differences between mice and humans<sup>[143,160]</sup>. Macrophages exhibit remarkable plasticity and phenotypic heterogeneity and different subsets have distinct and sometimes opposite properties (pro- *vs* anti-inflammatory, pro- *vs* antifibrotic). Further, environmental factors including cytokines control the polarization of macrophages but are not well defined. It is very likely that the functionality of hepatic macrophage subsets is also influenced by the nature of the underlying liver disease and this will hinder their use in an etiology independent manner. Another challenge for translating findings from murine models to humans is the fact that murine and human monocyte/macrophage subpopulations do not share the same surface-marker profiles. However new technologies including single cell RNA-Seq can help to de-convolute macrophage heterogeneity and may enable the development of specific therapies. Further, clarifying the basis of modulation of epigenetic and metabolic programs in macrophages can guide therapeutics. Delivery modalities represents another challenge, with multiple delivery platforms having been explored including nanoparticles, liposomes and oligopeptide complexes. These methods can be used to target macrophages for delivery of agents such as gene-silencing siRNA and miRNA inhibitors. While CRISPR-Cas9 technology might revolutionize medicine, their application for modulating macrophage biology is not well explored.

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## CONCLUSION

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Macrophages play a central role at all stages of MAFLD and contributes to the pathology in extrahepatic sites that are simultaneously affected. Thus, macrophage directed therapeutics have unique potential in MAFLD, but their heterogeneity represents a challenge. Metabolic and epigenetic programming and gene-based therapies are attractive approaches to manipulate macrophage function for clinical benefit, though the optimal delivery methods are still not defined. In the future, combined approaches consisting of multiple drugs that target different key pathways are likely to provide a better strategy to treat MAFLD. It remains to be elucidated

which combinations should to be used, but macrophage targeted therapies are one viable option.

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