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Review

Immunological mechanisms in steatotic liver diseases: An overview and clinical perspectives

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Steatotic liver diseases (SLD) are the principal worldwide cause of cirrhosis and end-stage liver cancer, affecting nearly a quarter of the global population. SLD includes metabolic dysfunction-associated alcoholic liver disease (MetALD) and metabolic dysfunction-associated steatotic liver disease (MASLD), resulting in asymptomatic liver steatosis, fibrosis, cirrhosis and associated complications. The immune processes include gut dysbiosis, adipose-liver organ crosstalk, hepatocyte death and immune cell-mediated inflammatory processes. Notably, various immune cells such as B cells, plasma cells, dendritic cells, conventional CD4$^+$ and CD8$^+$ T cells, innate-like T cells, platelets, neutrophils and macrophages play vital roles in the development of MetALD and MASLD. Immunological modulations targeting hepatocyte death, inflammatory reactions and gut microbiome include N-acetylcysteine, selonsertib, F-652, prednisone, pentoxifylline, anakinra, JKB-121, HA35, obeticholic acid, probiotics, prebiotics, antibiotics and fecal microbiota transplantation. Understanding the immunological mechanisms underlying SLD is crucial for advancing clinical therapeutic strategies. **(Clin Mol Hepatol 2024;30:620-648)**

Keywords: Liver diseases; Immunity; Dysbiosis; Adipose tissue

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INTRODUCTION

Excessive alcohol consumption and a high-calorie diet are two major etiologic factors for chronic steatotic liver disease (SLD), including metabolic dysfunction-associated alcoholic liver disease (MetALD)[1] and metabolic dysfunction-associated steatotic liver disease (MASLD).[2] Meanwhile, the development of MetALD and MASLD increases the burden of cirrhosis and liver cancer[3] and becomes leading causes of death worldwide.[4] It is imperative to thoroughly dissect the pathophysiology of MetALD and MASLD in detail, which promotes the development of new therapeutic modalities and alleviates the socioeconomic burden associated with liver diseases.[5]

The role of immunity in promoting inflammation and the progression of MetALD and MASLD has been demonstrated through continuous accumulation of clinical and experimental research.[6] In the development of MetALD and MASLD, the liver is not an isolated organ but rather undergoes complex interactions with other organs, such as adipose tissue and intestines, through blood circulation and immune cells. For example, alcohol, metabolites of ethanol, microbes and microbial metabolites damage the gastrointestinal tract and adipocytes, subsequently disrupting the immune system in MetALD.[7] Furthermore, the dysfunction of the immune system contributes to the formation of MASLD.[2]

Importantly, abnormal aggregation of hepatic immune cells leads to uncontrolled inflammatory reactions and liver injury in MetALD and MASLD. The complex interplay between multiple immune cells and hepatocytes, such as hepatic stellate cells (HSCs) and hepatic sinusoidal endothelial cells, plays a crucial role in disease progression.[8] For example, dysregulated metabolism in MetALD and MASLD affects the activation and proliferation of immune cells such as T cells, B cells, macrophages, neutrophils, dendritic cells (DCs), natural killer (NK) cells, and natural killer T (NKT) cells.[9,10]

In this review, we focus on the impact of immunity in MetALD and MASLD, along with the possible clinical mechanisms involved in affecting intestinal disorders, the adipose-liver axis, accelerating hepatocyte death and affecting immune cell-mediated inflammatory processes. In particular, we also discuss recent advances in pathways regulating multiple immune cells and corresponding immunological modulations in MetALD and MASLD. In conclusion, the liver is an immune organ that undoubtedly plays a key role in the pathology of SLD.

IMMUNOLOGICAL MECHANISMS IN SLD

The mechanisms underlying the pathogenesis of MetALD and MASLD differ in some ways, but the immune system plays an indelible role in both diseases.[11] The immunity in MetALD and MASLD is complex and multifactorial, involving the gut-liver axis,[12,13] adipocyte-liver axis,[14,15] adaptive and innate immune cells,[15,16] and increased inflammatory cytokines released by hepatocytes, adipocytes and mucosal immune cells (Fig. 1).[17]

Immunological mechanisms in MetALD

In terms of MetALD, hepatotoxicity induced by alcohol and oxidative stress are the major factors leading to immune responses.[18] However, studies suggest that immune responses may also play a key role in the development of MetALD,[19] especially in its inflammatory condition, alcoholic

steatohepatitis (ASH).[20] Immune involvement in the patho-genesis of MetALD involves multiple organs and pathways, mainly including gut microbiota and microbiota products, adipose tissue, and hepatocytes.[21]
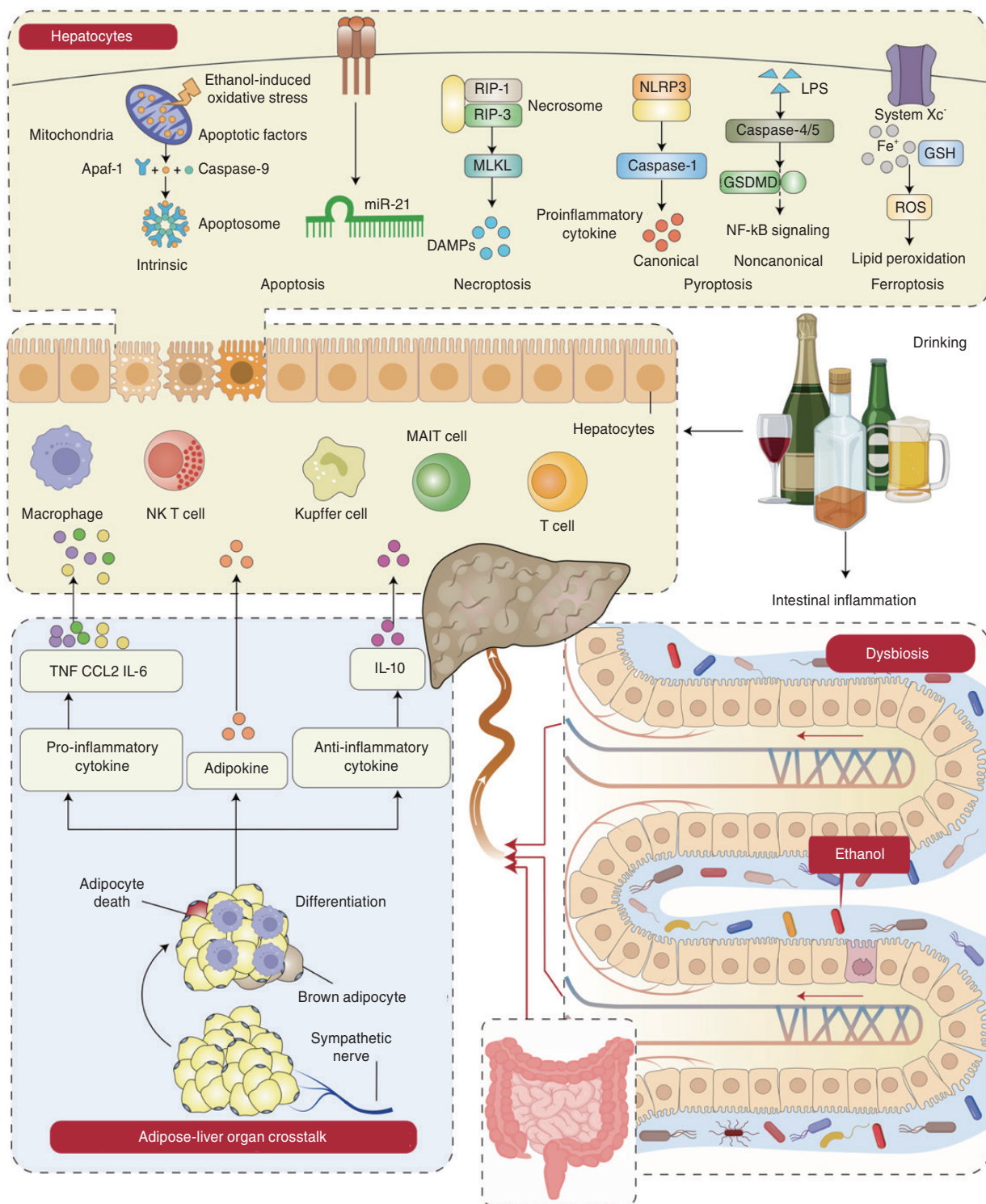

Figure 1. Continued.

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Figure 1. Immune dysregulation in MetALD through the interaction of the gut, liver, and adipose organs. The immune dysregulation in MetALD involves hepatocyte death, the adipocyte-liver axis and gut dysbiosis. (1) Chronic alcohol damages the intestinal barrier, increases intestinal permeability, and triggers an immune response. The dysfunctional gut barrier and products released by gut microbiota lead to the transfer of components and metabolites to the liver and initiate an immune reaction through the biliary system and portal vein communicating with the liver via the gut-liver axis.[27] (2) The crosstalk between adipose and liver organs is mediated by various factors, including neurotransmitters, pro-inflammatory cytokines (e.g., TNF, CCL2, IL-6), anti-inflammatory cytokines (e.g., IL-10), miRNAs, extracellular vesicles (EVs), metabolites, and adipocytokines. This crosstalk promotes hepatocyte damage and inflammation in MetALD.[38] (3) Excessive alcohol consumption can lead to various types of hepatocyte death, such as apoptosis, necroptosis, pyroptosis, and ferroptosis. Hepatocyte apoptosis involves the secretion of apoptosis factors that combine with apaf-1 and caspase-9 to form the apoptosome (intrinsic) and cell apoptosis through miR-21 (extrinsic).[50,51] Hepatocyte necroptosis involves RIP1 and RIP3 activation and subsequent MLKL phosphorylation, leading to DAMPs.[54,55] Canonical pyroptosis depends on caspase-1 and is mediated by the NLRP3 inflammasome, inducing the release of proinflammatory cytokines.[57] Noncanonical pyroptosis is activated by LPS and then activates caspase-4/5 and GSDMD, which regulates NF-κB signaling.[61] Ferroptosis is an iron-dependent cell death mechanism characterized by glutathione (GSH) depletion and damage to system Xc-, leading to cell death through ROS accumulation and lipid peroxidation.[63] These factors activate mucosal immune cells such as macrophages, NK T cells, KCs, MAIT cells and T cells releasing proinflammatory cytokines and chemokines, ultimately leading to hepatocyte death. MetALD, metabolic dysfunction-associated alcoholic liver disease; CCL2, Chemokine (CC-motif) ligand 2; IL, interleukin; RIP-1/3, receptor interacting protein-1/3; MLKL, mixed lineage kinase domain like; DAMPs, danger associated molecular patterns; NLRP3, NACHT, LRR, and PYD domains-containing protein 3; LPS, lipopolysaccharide; GSDMD, gasdermin D; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; KCs, Kupffer cells; MAIT, Mucosal Associated Invariant T cells.

The main mechanism is as follows: (1) Alcohol intake damages the intestinal barrier, allowing gut-derived metabolites or gut microbiota itself to reach hepatocytes. This triggers an immune response by disrupting communication between the gut and liver through effects on the gut-liver axis, biliary system and portal vein system.[19,22] (2) Alcohol consumption alters adipose tissue secretion of adipokines, pro-inflammatory, anti-inflammatory cytokines and adipokines to activate immune cells, leading to liver inflammation and deterioration of fibrosis.[23] (3) The immune response leads to various types of hepatocyte death, such as apoptosis, necroptosis, pyroptosis, and ferroptosis, affecting the severity of liver inflammation and the progression of MetALD.[24]

Gut dysbiosis in MetALD

The gut microbiota maintains the integrity of the intestinal barrier, regulating intestinal homeostasis and stimulating host immune responses.[25] Intestinal barrier integrity and gut microbiota and their metabolites are necessary for regulating MetALD progression.[26] The intestine communicates with the liver through the biliary system and portal vein via the gut-liver axis, transferring intestinal-derived metabolic substances or intestinal microbiota itself to the liver and stimulating immune reactions in MetALD progression.[27] For example, antibiotics alleviate alcohol-induced intestinal tight junction damage and inflammatory activation.[28] Probiotic compounds reverse the gut dysbiosis induced by MetALD and maintain the integrity of the intestinal barrier, thus reducing liver injury, mainly by upregulating the production

of mucus and the expression of tight junction proteins.[29] Additionally, intestinal bacterial metabolites such as short-chain fatty acids can penetrate into the blood and then modulate immune cells such as DCs precursors in the bone marrow.[30] Commensals regulate both innate and adaptive immune systems to establish sustained tolerance to innocuous antigens. Innate lymphocytes are often located in peripheral tissues and are regulated by microbiota.[31] Adaptive lymphocytes are also influenced by gut microbes, such as B cells generating IgA controlled by microbes, T_H17 cells regulated by segmented filamentous bacteria, regulatory T (Treg) cells modulated by *Clostridia*, and T follicular helper cells influenced by *Akkermansia muciniphila*.[32]

Adipose-liver organ crosstalk in MetALD

Ethanol is likely unique among toxins in that it perturbs almost all aspects of hepatic adipose tissue, partly due to the enormous metabolic demand of alcohol metabolism on the liver.[33,34] Alcohol-induced adipose injury is regulated by the release of mediators containing pro-inflammatory and anti-inflammatory cytokines and adipokines. For instance, after consuming ethanol, the differentiation of preadipocytes and the production of adipokines by adipocytes are impaired,[35] leading to adipose tissue inflammation and adipocyte death.[36,37] These factors result in insulin resistance in adipose tissue, increased lipolysis and the production of pro-inflammatory cytokines,[38] especially TNF, IL-1β, CCL2, IL-10 and IL-18 production. These factors are positively correlated with the severity of MetALD.[38-40] In addition, multiple

immune cells are present in adipose tissue, including macrophages, DCs, neutrophils, T cells and B cells, which are affected by excessive alcohol intake and toll-like receptors (TLR)4 expression.[41] Moreover, excessive alcohol intake alters the adipokine secretion of leptin, visfatin, resistin, and adiponectin to activate both Kupffer cells (KCs) and HSCs, leading to liver inflammation and fibrosis formation.[42,43] A recent study found that excessive drinking increases the expression and activity of uncoupling protein 1 (UCP1) in brown adipose tissue.[44] Brown adipose tissue and beige fat oxidize fatty acids to provide fuel for UCP1-mediated thermogenesis, thus inhibiting lipid transport to the liver. The deletion of the UCP1 gene exacerbates alcohol-induced liver steatosis, injury, inflammation, and fibrosis.[45,46] Acute adipocyte death causes liver injury and activates inflammation in a chemokine (C-C motif) receptor 2-positive (CCR2+) macrophage-dependent manner, further increasing the sensitivity of hepatocytes to lipotoxicity.[47] Therefore, adipose-liver crosstalk plays a role in increasing liver inflammation and injury in MetALD. However, for future clinical considerations, it is necessary to continuously explore more potential mechanisms.

Hepatocyte death crosstalk in MetALD

Excessive alcohol consumption can result in various types of hepatocyte death, such as apoptosis, necroptosis, pyroptosis, and ferroptosis, which are closely linked to the severity of inflammation in MetALD.[48] Ethanol is metabolized by alcohol dehydrogenase, cytochrome P450 family 2, subfamily E, polypeptide 1 (CYP2E1) and catalase, leading to the production of reactive oxygen species (ROS).[49] Ethanol-induced oxidative stress activates the mitochondrial (intrinsic) apoptosis pathway, involving the release of apoptosis factors like cytochrome c and apoptosis-inducing factors into the cytosol. These factors combine with apoptotic protease activating factor 1 (apaf-1) and caspase-9 to form the "apoptosome", finally activating the internal apoptotic pathway.[50,51] Therefore, apoptotic cells are efficiently engulfed by surrounding macrophages, contributing to the non-inflammatory nature of the MetALD pathway. Prolonged alcohol exposure triggers death receptor-mediated (extrinsic) cell apoptosis pathways, including Fas ligands and TNF-α, and induces cell apoptosis through miR-21.[52] Hepatocyte stress is a result of ethanol metabolism and increased exposure to gut-derived pathogen-associated molecular patterns (PAMPs) and endogenous danger-associated molecular patterns (DAMPs), establishing a close link to necroptosis.

The characteristics of necroptosis include damage to the structure of the cell membrane, nucleus, and cytoplasm to varying degrees, increased permeability of the cell membrane, deformation and dissolution of the nucleus, and loss of activity in enzymes and proteins in the cytoplasm during the progression of MetALD. Necroptotic cells release various damage-associated molecular patterns (DAMPs) that trigger inflammatory responses.[53] The process is regulated by the activation of receptor-interacting protein (RIP) 1 and RIP3, which is partially induced by the necrosome complex and subsequent phosphorylation of mixed lineage kinase domain like (MLKL).[54,55] As a result, necrotic liver cell death is immunogenic, leading to excessive inflammation and hepatocyte death by activating innate immune cells or inducing other forms of hepatocyte death, such as pyroptosis.[56]

Pyroptosis also plays a crucial role in the progression of MetALD. Canonical pyroptosis relies on caspase-1 and is facilitated by inflammatory bodies, such as the NLR family pyrin domain-containing 3 (NLRP3),[57] resulting in LPS-induced ER stress in hepatocytes.[58] Similarly, the absence of NLRP3 can ameliorate liver steatosis and chronic ethanol damage.[59] Moreover, pyroptosis triggered by intestinal PAMP and metabolic DAMP, such as uric acid and adenosine triphosphate, leads to the secretion of inflammasome-dependent cytokines by immune cells damaged by ethanol.[60] Additionally, LPS can directly trigger noncanonical pyroptosis signaling independently of TLR4. Mechanistically, activated caspase-11 or caspase-4/5 in the liver detects intracellular LPS, cleaves gasdermin D (GSDMD) within its linker ring, binds to phosphoinositol on the plasma membrane, cleaves it, and ultimately induces cell death. Furthermore, GSDMD regulates adipogenesis, inflammatory response, and nuclear factor kappa B (NF-κB) signaling, all of which are critical in the progression of MetALD.[61]

Ferroptosis is induced in hepatocytes treated with ethanol.[62] Excessive alcohol consumption promotes an increase in serum ferritin concentration and transferrin saturation, leading to an increase in liver iron reserves.[63] Ferroptosis is an iron-dependent oxidative programmed cell death mechanism characterized by glutathione (GSH) depletion, damage to the glutamate antiporter (system Xc-), and overexpression of lipid hydroperoxides.[64] This process

produces oxygen and causes local inflammation in the liver.[65] Subsequently, the inactivation of glutathione peroxidase 4, which can reduce lipid peroxides in the plasma membrane, leads to cell death through the accumulation of ROS caused by excessive iron-induced lipid peroxidation or the Fenton reaction.[66] These reactive hydroxyl radicals destroy the lipid membrane, induce lipid peroxidation and membrane instability, and eventually lead to the leakage of cell substances and cell death.[67]

All in all, the immunological mechanisms in MetALD are complex and multifactorial, involving hepatocyte death, adipose-liver organ crosstalk disorder, and intestinal disturbance caused by excessive alcohol intake. However, the mechanisms between MetALD and MASLD are quite different.

Immunological mechanisms in MASLD

The spectrum of MASLD includes steatosis, metabolic dysfunction associated steatohepatitis (MASH), fibrosis, cirrhosis, and MASH associated hepatocellular carcinoma (HCC).[68,69] Recent research suggests the "multiple hit" hypothesis for the development of MASLD, indicating that immunological mechanisms in the liver, intestines, and adipose tissue influence the progression of MASLD.[5]

The main mechanisms include: (1) Damage to the intestinal barrier results in the transfer of bacteria or bacterial components into the bloodstream, which is necessary for liver inflammation and the progression of MASLD.[70] (2) Adipose tissue plays a key role in regulating MASLD progression by releasing adiponectin, leptin, lipid moieties and lipid substances like tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and calprotectin such as S100A8 and S100A9.[71] (3) Different immune cells produce various cytokines and chemokines, such as TNF-α, IL-1 and IL-18 (Fig. 2).[16]
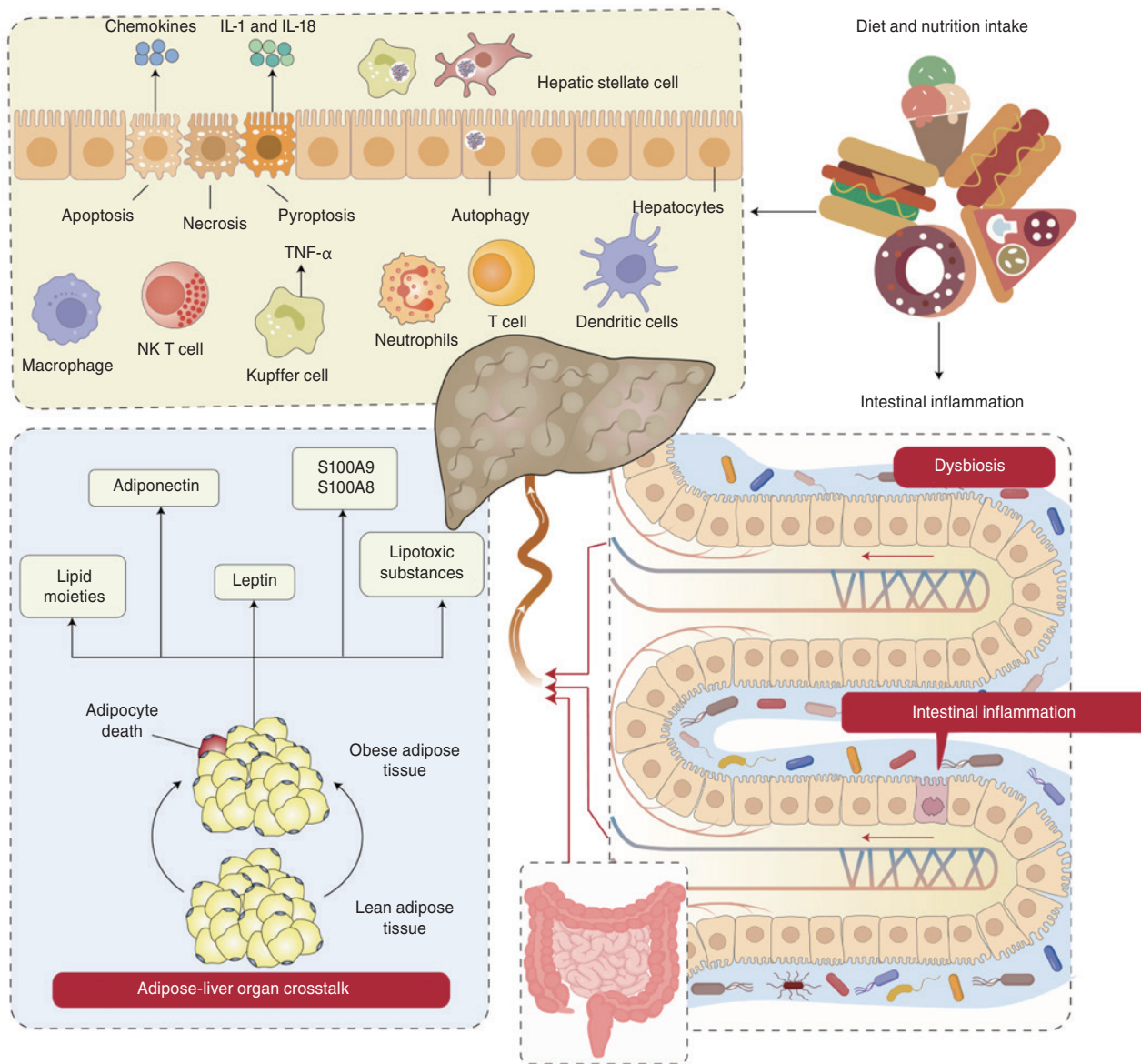
Gut dysbiosis in MASLD

Gut microbiota is also essential for the progression of MASLD.[12] The intestines and liver communicate through tight junction interactions via the biliary tract, portal vein and systemic circulation. This communication allows gut-derived products to be directly transported to the liver, while the liver provides feedback on bile and antibody secretion to the intestine.[8] An unhealthy state of gut microbiota in MASLD patients is characterized by a high abundance

of pathogens such as *Escherichia coli*, *Campylobacter jejuni*, *Salmonella enterica*, *Vibrio cholerae*, and *Bacteroides fragilis* and a low abundance of key genera including *Bacteroides*, *Prevotella* and *Ruminococcus,* which represents an unhealthy state for gut microbiota in MASLD patients.[72,73] Furthermore, MASLD is associated with intestinal inflammation, where the number of immune cells in the intestinal mucosa, such as CD4$^+$ and CD8$^+$ T lymphocytes, is reduced. This reduction is linked to increased cytokine secretion, leading to the breakdown of the tight junctions in the intestinal barrier.[74]

Bile acid metabolism is completed under the influence of gut microbiota, and the enzymes produced by gut microbiota play a crucial role in the enterohepatic circulation of bile acids.[75] Additionally, bile acids regulate the size and composition of gut microbiota.[76] These interactions between bile acids and intestinal microbiota significantly impact lipid metabolism and the progression of MASLD,[77] consequently influencing the immune response. Bile acids also influence the differentiation of T cells and the polarization of macrophages. The metabolism of bile acids and a distinct lymphocyte population collectively maintain the integrity of the intestinal barrier system, with Treg cells expressing forkhead box protein P3 (FOXP3) contributing to the homeostasis of the intestinal immune system. Furthermore, bile acids promote the polarization of macrophages towards the M1 phenotype, partly through the transactivation of TLR2 by M2 muscarinic acetylcholine receptor, leading to an increased production of pro-inflammatory cytokines.

In addition, the development of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) is encouraged by immunity, which is linked to changes in the gut microbiota, particularly the activity of LPS.[78] These factors then cause the production of cytokines, chemokines, and growth factors by stimulating and activating TLRs and inflammasomes. These occurrences promote the recruitment, activation, and differentiation of monocytes into tumor-associated macrophages, which leads to angiogenesis and fibrosis and works in concert with cancer-associated fibroblasts.[79] Furthermore, HSCs activation and differentiation into myofibroblast-like cells exacerbate fibrogenesis. Moreover, active HSCs promote T-reg activation while impairing the capacity of Natural Killer cells (NKs) to induce HSC death, hence impairing immuno-tolerance.[80] The aforementioned macrophages,

Figure 2. Immune dysregulation in MASLD through the interaction of the gut, liver, and adipose organs. The immune dysregulation in MASLD involves hepatocyte death, the adipocyte-liver axis and gut dysbiosis. (1) High fat diets (HFD) consumption leads to gut barrier dysfunction, escalating intestinal inflammation and triggering an ectopic immune response. Damage to the intestinal barrier facilitates the passage of bacteria or bacterial components into the bloodstream, essential for hepatocyte death and MASLD progression.[12] (2) HFD consumption transforms lean adipose tissue into obese adipose tissue. Obese adipose tissue releases adiponectin, leptin and lipid moieties like palmitic acids, ceramide, IL-6 and TNF, inducing cell stress and hepatocyte death in MASLD.[83,84] (3) Both gut dysbiosis and obese adipose tissue lead to hepatocyte death, which mainly encompasses apoptosis, necroptosis and pyroptosis. These factors activate KCs, producing TNF, TRAIL and FAS ligands by engulfing apoptotic bodies, thereby stimulating the secretion of chemokines and triggering hepatocyte apoptosis.[96] These factors further damage hepatocytes, leading to necroptosis and pyroptosis. This process involves the release of IL-1 and IL-18 into the bloodstream, influencing autophagy alterations in hepatocytes and nonparenchymal cells like KCs and HSCs.[103] All these factors then activate the mucosal immune cells such as macrophages, NK T cells, Kupffer cells, neutrophils, T cells and DCs to release inflammatory cytokines and chemokines, further leading to hepatocyte death. MASLD, metabolic dysfunction-associated steatotic liver disease; IL, interleukin; KCs, Kupffer cells; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; HSCs, hepatic stellate cells; DCs, dendritic cells.

which can stimulate a T_H2 immune response and result in an immuno-tolerance status, also aid in these last steps.

All the processes mentioned above exacerbate and advance MASLD development.[81]

Adipose-liver organ crosstalk in MASLD

Adipose tissue is the largest endocrine organ in the body, involved in various physiological and pathological processes such as energy metabolism, endocrine homeostasis, and inflammatory reactions. Adipose-liver crosstalk influences systemic metabolism and insulin resistance.[82] Recent studies have revealed that adipose tissue not only serves as the primary source of fatty acids in the liver but also plays a crucial role in regulating MASLD progression by releasing adiponectin, leptin, lipid moieties, lipotoxic substances and calprotectin.[83,84] Adiponectin inhibits the proliferation of HSCs,[85] while leptin triggers inflammation by activating KCs and enhancing their release of TNF-α.[86] Additionally, lipid moieties like palmitic acids and ceramide released by adipocytes inhibit the functions of the endoplasmic reticulum (ER) and mitochondria, causing cell stress and eventual hepatocyte death.[87] Furthermore, lipotoxic substances and calprotectin (S100A8 and S100A9) from adipose tissue stimulate infiltrating macrophages[88] and KCs[89] through TLR4 and NLRP3 signaling.[90,91] These processes result in the release of inflammatory factors from adipose tissue, such as TNF-α, leading to hepatocyte death and activation of KCs through JNK pathways.[92,93] A recent study demonstrated that acute adipocyte death triggers lipolysis by activating chemokine receptor 2-positive CCR2+ macrophages and increasing epinephrine and norepinephrine levels.[94] Therefore, adipose-liver crosstalk contributes to the escalation of liver inflammation and injury in MASLD.[33] However, for future clinical considerations, a comprehensive understanding of adipose-liver crosstalk is essential to continually explore additional potential mechanisms.
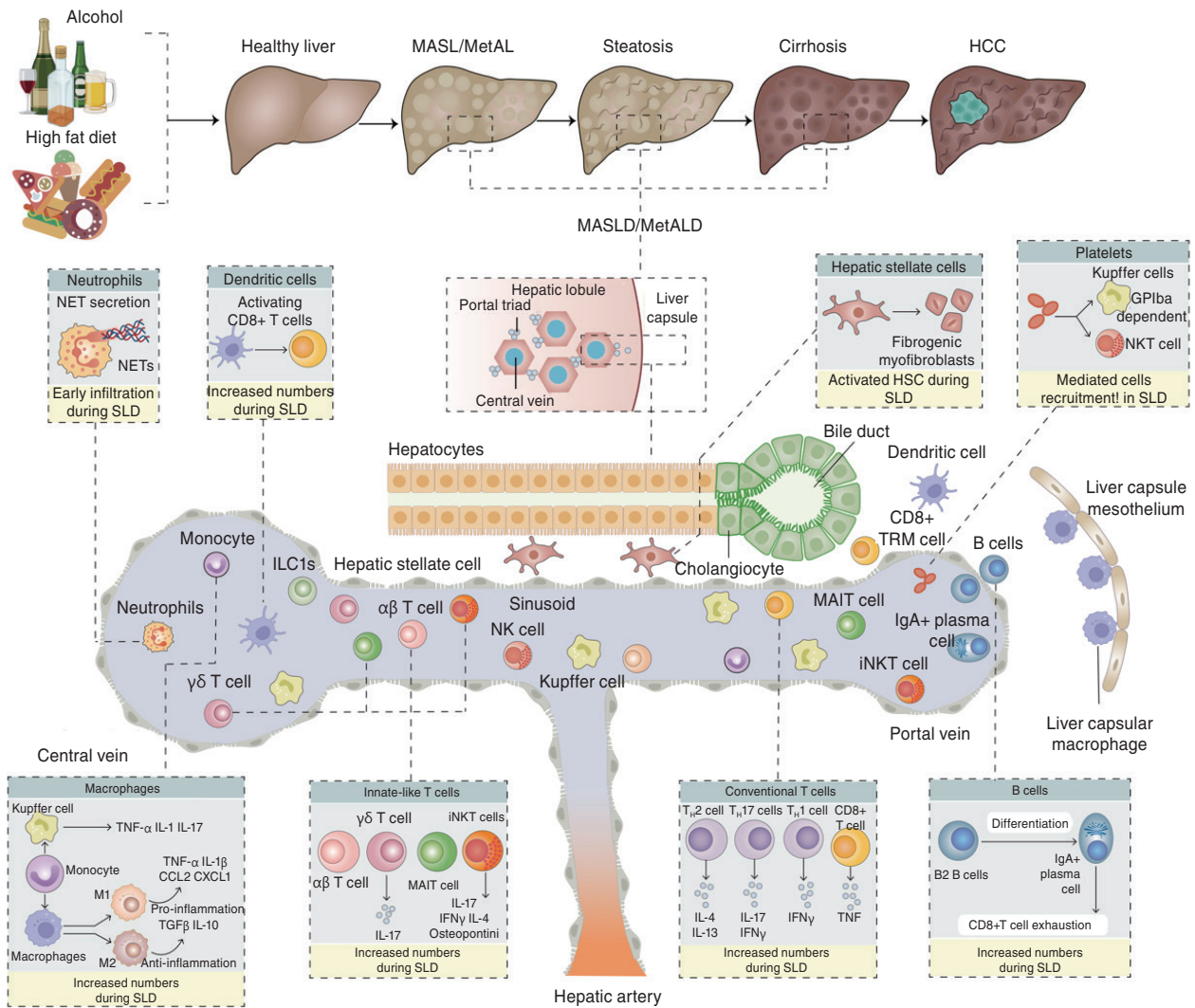
Hepatocyte death in MASLD

Hepatocyte death is a major factor contributing to the progression of MASLD.[95] Various mechanisms of hepatocyte death, such as apoptosis, necroptosis, and pyroptosis, play a crucial role in the development of MASLD.[96] Hepatocyte apoptosis leads to the release of DNA fragments from apoptotic bodies, activates HSCs, and contributes to fibrosis formation, making it a significant contributor to MASLD.[97] Furthermore, hepatocyte death induced by death receptors like TRAIL stimulates the release of extracellular vesicles (EVs) and certain chemokines, which in turn enhance the recruitment and activation of the immune sys-

tem.[98,99] Additionally, by engulfing apoptotic particles, KCs release TNF, TRAIL, and FAS ligands, thereby accelerating hepatocyte death and leading to hepatitis and fibrosis.[96] Necrosis, a regulated form of programmed cell death, is mediated by a combination of RIP1 and RIP3. In MASLD, increased RIP3 expression is associated with JNK activity and inflammation,[100,101] and hepatic inflammation and liver fibrosis are significantly reduced with RIP3 deficiency.[102] Pyroptosis, a recently identified form of caspase 1-dependent cell death, activates the inflammasome, leading to the release of IL-1 and IL-18, and continuous release of cytoplasmic contents.[103] The circulation of IL-1 and IL-18 activates the immune system.[104] Several studies suggest that altered autophagy in hepatocytes and nonparenchymal cells like KCs and HSCs contributes to the pathophysiology of MASLD.[105] For example, dysregulated unfolded protein response (UPR) in hepatocytes led to apoptosis and inflammation in mice.[106] Moreover, reduced liver autophagy results in inadequate clearance of damaged mitochondria, leading to MASLD-related oxidative stress, release of mitochondrial factors, hepatocyte death and liver inflammation.[107] In animal models of MASLD, inhibiting IL-1 signaling reduced liver fibrosis, inflammation, steatosis and hepatocyte death.[108]

In summary, the immunological mechanisms in MASLD are complex and multifactorial, involving hepatocyte death, adipose-liver organ crosstalk disorder, and intestinal disorder induced by metabolic dysfunction. These factors subsequently impact the accumulation of immune cells in the liver.

IMMUNE CELLS-INDUCED IMMUNE DYSREGULATION IN SLD

The liver, the largest immune organ, houses a variety of innate and adaptive immune cells, such as macrophages, KCs and lymphocytes.[109] These cells possess immunological functions and can eliminate viruses, bacteria, and specific antigens from the body. Moreover, the liver's high level of vascularization, combined with reduced blood flow in its fenestrated capillary-like sinusoids, creates a unique environment that promotes immune cell exposure to blood-borne and intestinal infections.[16,110] The liver contains a wide range of immune cells, including lymphoid and my-

Figure 3. Immune modulations of SLD pathogenesis. The hepatic immune cell repertoire is altered and participates in the uncontrolled inflammatory environment that promotes hepatocyte death and liver fibrosis. These immune cells include innate-like T cells, such as iNKT cells, MAIT cells and γδ T cells, as well as conventional CD8^{+} T cells and CD4^{+} T cell subsets, including IFNγ-producing T$_H$1 cells,[156] IL-4- and/or IL-13-producing T$_H$2 cells,[169] and IL-17-producing T$_H$17 cells.[157] NETs are secreted or released during NETosis. Neutrophil accumulation is a precursor to SLD that causes inflammation and liver damage.[189,190] The population of DCs and type 1 conventional DCs (cDC1s in particular) increases, promoting hepatic damage and liver inflammation by activating CD8^{+} T cells.[131,132] Monocytes are also quickly recruited to the liver, where they can develop into pro-inflammatory macrophages or differentiate into KCs, which are derived from monocytes.[194,195] Platelets are more numerous and more active, which promotes liver steatosis, inflammation, and damage. This suggests that platelets may activate and directly bind to KCs in a glycoprotein GPIb-dependent manner. B lymphocytes, particularly IgA^{+} plasma cells, accelerate the development of SLD by exhausting CD8^{+} T lymphocytes, which is one of their immunosuppressive actions.[185,186] Additionally, the cytotoxic actions of fatty acids reduce the anti-injury potential of CD4^{+} T cells, promoting SLD progression to HCC.[142,143] Moreover, CD8^{+} T cells and, particularly, the auto-aggressive CXCR6^{+} subset promote liver damage and the SLD-HCC transition by secreting pro-inflammatory cytokines like TNF and directly killing hepatocytes in a FASL-dependent and TNF-dependent manner.[159,160] SLD, steatotic liver diseases; NKT cell, natural killer T cells; MAIT, Mucosal Associated Invariant T cells; IFNγ, interferon γ; NETs, neutrophil extracellular traps; SLD, steatotic liver diseases; DCs, dendritic cells; KCs, Kupffer cells; HCC, hepatocellular carcinoma.

eloid cell lineages, primarily situated in the sinusoids, intravascular spaces and subcapsular compartments (Fig. 3).[111]

Recent developments have improved our understanding of how the immune cell repertoire is altered during MetALD

and MASLD in mice, as well as in the cirrhotic liver of humans.[112] For example, significant changes in the myeloid compartment were observed in both mice and humans, accompanied by a notable influx of monocytes and cells origi-

nating from monocytes.[113] These alterations in the hepatic immune cell composition likely contribute to the uncontrolled inflammatory environment that exacerbates liver damage and progresses MetALD and MASLD.[114] Throughout these diseases, there is undoubtedly a complex interplay among various immune cell types, hepatocytes, HSCs, and liver sinusoidal endothelial cells.[115] However, the complexity of this interaction is still not fully understood, and our current knowledge is primarily based on the study of specific immune cell types in the pathogenesis of MetALD and MASLD, as shown in the following (Table 1).[116]

B cells and plasma cells in SLD

B cells generate immunoglobulins,[117] present antigens[118] and release cytokines[119] after activating pathogen-related molecular patterns mediated by TLR, impacting immune-mediated inflammatory responses in numerous ways.[120] In mice, B cells have pro-inflammatory properties in the SLD, which involves the adaptive immune mechanism mediated by B cell receptors and the myeloid differentiation primary response 88 (MyD88)-dependent innate immune mechanism.[121] In humans, B cells were activated concurrently with the beginning of steatohepatitis, developed into plasmablasts and plasma cells, and then accumulated in SLD with

lobular inflammation and fibrosis.[122] Furthermore, B cells may be influenced by the increase in intestinal permeability and inflammatory mediators produced by the microbiota. Finally, decreased inflammation and fibrosis in B-cell defective animals resulted in a reduction in SLD severity.[121,123]

B cells can be categorized into two main lineages based on their heterogeneity.[124] In secondary lymphoid organs, B2 cells are activated and supported by CD4$^+$ T helper (TH) cells to generate high-affinity antibodies that target specific antigens. As part of an innate-like immune response, B1 cells produce "natural" antibodies such as immunoglobulins encoded by the germline and present even without external antigen stimulation.[125] Depletion of B2 cells has been associated with a decrease in SLD-related hepatic fibrosis,[122] although the exact role of B1 cells in SLD remains unknown. Serum levels of B cell-activating factor (BAFF), a cytokine that regulates B2 cell development and survival but not B1 cell survival,[126] are elevated in SLD patients and further increased in those with fibrosis. In mice, neutralizing BAFF reduced liver damage in SLD.[127]

B2 cells undergo differentiation after activation to become plasma cells or long-lived B cells that produce antibodies.[128] The liver is particularly abundant in plasma cells that produce IgA, IgG, or IgE, the number of these cells increases during SLD.[129] Moreover, patients with SLD had in-

Table 1. Immune cell populations in SLD pathogenesis

Cell type	Relative increase/ Decrease	Function	Reference
B cells	+	Promoting the differentiation of B2 B cells into IgA$^+$ plasma cells and exhausting CD8$^+$ T lymphocytes	117, 120
DCs	+	Stimulating CD4$^+$ T cells	131, 132
CD4+ T cells	+	Differentiating T_H1, T_H2 and T_H17 cells and releasing cytokines	142, 143
CD8+ T cells	+	Producing IFN, TNF and cytotoxic chemicals	159, 160
iNKT cells	+	Producing IFN, IL-4, osteopontin and IL-17	172, 173
γδ T cells	+	Releasing IL-17 and cause hepatic damage	178
MAIT cells	+	Regulating anti-inflammatory macrophages	180, 181
T_H1 cells	+	Producing IFNγ	156
T_H17 cells	+	Producing IFNγ and IL-17	157
T_H2 cells	+	Producing IL-4 and IL-13	169
Platelets	+	Releasing GPIbα and boosting NKT cell recruitment leading to cell aggregates	185, 186
Neutrophils	+	Producing ROS, cytokines, proteases, and NETs	189, 190
Macrophages	+	Developing into pro-inflammatory macrophages or differentiate into KCs	194, 195

SLD, steatotic liver diseases; IFNγ, interferon γ; IL, interleukin; NKT cell, natural killer T cells; ROS, reactive oxygen species; NETs, neutrophil extracellular traps; KCs, Kupffer cells; DCs, dendritic cells; MAIT, Mucosal Associated Invariant T cells.

creased numbers of activated intestinal B-cells and showed a positive correlation between IgA levels and activated Fc receptor gamma-chain in hepatic myeloid cells as well as the degree of liver fibrosis.[130] However, although there is ample evidence linking B cells and IgA to SLD pathophysiology, more research on the underlying mechanisms is necessary. More research is needed to determine the antigen specificity of the B cells that are produced in SLD patients and are involved in the development of the disease.

Dendritic cells in SLD

DCs play a significant role in directing hepatic immunity. The plasmacytoid and myeloid subsets of DCs, which constitute less than 1% of all hepatic myeloid cells, are further categorized into type 1 and type 2 DCs.[131] The onset of SLD is associated with the expansion of myeloid DCs and their ability to specifically stimulate $CD4^+$ T cells, triggering an adaptive immune response.[132] DCs contribute to local inflammation by recognizing various PAMP, including TLR and other pattern-recognition receptors.[133,134] While both $CD103^+$ cDC1s and $CD11b^+$ cDC2s subsets of conventional DCs are present in the liver and increase during SLD in mice, their specific roles in the disease's pathophysiology remain unclear.[135] In humans, individuals with SLD exhibit higher levels of cDC1s in their livers, and an increase in cDC1s was associated with more SLD-specific symptoms. Activation of SLD in ATF-Like-3-deficient animals lacking cDC1s leads to elevated liver triglyceride levels but comparable levels of liver damage.[136,137] Similarly, SLD induction in ATF-Like-3-deficient mice lacking cDC1s leads to increased liver triglyceride levels but similar liver injury levels.[138,139] However, this whole-body deletion of ATF-Like-3 may have influenced SLD independently of cDC1 loss. Using a more precise cDC1 depletion model, cDC1s induce liver damage in mice, although the mechanisms are still not fully understood.[140] On the other hand, the role of cDC2s in SLD has not been explored yet. In conclusion, further research is needed to comprehensively comprehend the role of cDCs in SLD pathogenesis and the associated mechanisms.

Conventional CD4+ and CD8+ T cells in SLD

Conventional $CD4^+$ T_H cells play a crucial role in immune surveillance and adopt various specialized cell fates through interactions with specific DC subpopulations and cytokine environments.[141] T_H1, T_H2 and T_H17 cell fates are distinguished by the production of interferon-γ (IFNγ), IL-4 and/or IL-13 and IL-17, respectively.[142] The roles of these cytokines and their signaling pathways have been studied in SLD.[143] As these cytokines are also secreted by cell types other than $CD4^+$ T cells, it is challenging to definitively attribute the observed phenotype to alterations in the T_H cell population. Therefore, further research is necessary to enhance our comprehension of this aspect.

Mice lacking IFN, the prototype T_H1 cell cytokine, had a substantial inhibition of macrophage inflammatory response and further suppressed HSCs activation and liver fibrosis.[144] Reduced fibrosis in these animals is related to much lower production of osteopontin, a recognized inducer of liver fibrogenesis, although its mechanisms are still mostly unclear.[144] Other cell types that produce IFN, such as $CD8^+$ T cells, contribute to the phenotype.[145] Additionally, CXCL10, an IFN-inducible chemokine, is also implicated in SLD etiology.[146] CXCL10 causes CXCR3-expressing cells, including T lymphocytes, to chemotaxis.[147] CXCL10 levels in the blood are elevated in SLD patients, and CXCL10 deletion or antibody-mediated CXCL10 neutralization reduces steatosis, liver damage, and fibrosis in rats.[148] CXCR3 deficiency decreased the development of SLD. Thus, reduced CXCL10-CXCR3 signaling may help to explain the impact of IFN insufficiency on SLD.

It has also been discussed how several cytokines linked to T_H2 cells affect SLD.[149] Higher serum levels of IL-13, and their livers have higher levels of IL-13RA2 expression in SLD. HSCs express IL-13RA2, and the clinical characteristics of SLD are ameliorated by cytotoxin-mediated death of $IL-13RA2^+$ cells. Patients with SLD have higher serum levels of IL-13 and higher liver expression levels of its receptor, IL-13RA2.[150] IL-33 induces the secretion of type 2 cytokines IL-4, IL-5, and IL-13, which is consistent with the recognized involvement of type 2 cytokines in extracellular matrix synthesis.[151] IL-33 therapy also contributes to tissue regeneration and fibrosis after injury in mice.[152] However, treatment with IL-33 restricts the buildup of hepatic triglycerides and results in a minor decrease in liver damage in a

mouse model of SLD.[153] In general, it is uncertain how T_H2 cell-mediated immunity is involved in SLD.

T_H17 cells cells perform various functions, including maintaining the gut barrier in response to commensals and contributing to inflammatory disorders in response to pathogens.[154] Patients with SLD show an increase in T_H17 cells and the expression of T_H17 cell-related genes.[155] In SLD mouse models, there is an elevation of T_H17 cells, particularly a subset of pro-inflammatory $CXCR3^+$ T_H17 cells that contribute to SLD.[148] SLD worsens in animals lacking the unconventional prefoldin RPB5 interactor (Uri1) in hepatocytes ($Hep^{\Delta Uri1}$ mice) due to DNA damage, which is linked to T_H17 cell differentiation and increased hepatic IL-17A production.[156,157] In $Hep^{\Delta Uri1}$ mice, blocking IL-17A with a monoclonal antibody or reducing T_H17 cells production with the RORγt inhibitor digoxin reduces the hallmarks of SLD. Lack of IL-17A provides protection, while administering recombinant IL-17A exacerbates hepatic DNA damage, steatosis, liver injury, and fibrosis in wild-type mice fed an SLD-inducing diet. Disrupted IL-17-induced signaling in myeloid cells shields $Hep^{\Delta Uri1}$ animals from SLD, suggesting significant communication IL-17-producing cells, especially T_H17 cells and phagocytes.[158] Depleting all $CD4^+$ T cells reduce hepatic fibrosis, aligning with the fibrosis-promoting effects of cytokines produced by T_H1, T_H2 and T_H17 cells as mentioned earlier.[143]

$CD8^+$ T cells are primarily responsible for the production of IFN, TNF and cytotoxic chemicals such as perforins.[159,160] In both mice and humans, the number of hepatic $CD8^+$ T cells increases during SLD, particularly $CD8^+$ T cells expressing CXCR6.[161] $CXCR6^+$ $CD8^+$ T lymphocytes stimulate hepatocyte death in a perforin-independent, FasL (CD95L)-dependent way. $CD8^+$ T cell depletion reduced liver damage in a diet-induced animal model of SLD. SLD symptoms were enhanced in perforin 1-deficient animals, which have a larger amount and activating state of hepatic $CD8^+$ T cells.[162] Perforin deficiency has been shown to promote $CD8^+$ T cell activation.[163,164] This action is cell-extrinsic and includes the survival of immunostimulatory DCs in the absence of antigen-loaded DCs being killed by perforin.[165,166] Furthermore, $CXCR6^+$ $CD8^+$ T cells that concentrate in SLD express the exhaustion marker PD1, block PD1 and increase the activation $CD8^+$ T cells, leading to faster SLD pathogenesis in mice.[167] As a result, $CD8^+$ T lymphocytes are expected to contribute to hepatic damage during SLD.

Overall, there is a lack of an integrated mechanism explaining how T cell subsets are activated and contribute to increased hepatic inflammation in SLD.[168] The majority of current research focuses on cytokines released by T cell subsets rather than on T cells themselves.[169] Furthermore, while $CD8^+$ T cell-mediated hepatocyte death develops in an antigen-independent manner during SLD, it is uncertain if adaptive, antigen-specific T cell responses are also involved.[170,171] More studies will be needed to fill these information gaps and discover how these pathways might be addressed therapeutically without compromising immune defenses.

Innate-like T cells in SLD

iNKT cells are generally concentrated in the liver relative to other organs and are significantly elevated in SLD disease progression.[172] CD1D-deficient or TRAJ18-deficient mice, in which iNKT cells do not mature, were used to study their function in SLD etiology.[173] iNKT cells enhance liver fibrosis by increasing osteopontin expression in the liver, which promotes fibrogenesis in SLD.[174,175] Recent research found that iNKT cells promote hepatic steatosis and, together with $CD8^+$ T cells, cause hepatic injury, leading to SLD progression.[176] $T\text{-bet}^+$ iNKT1 cells, $GATA3^+$ iNKT2 cells and $RORγt^+$ iNKT17 cells are all types of iNKT cells that generate IFN, IL-4 and IL-17, respectively.[177] Type 2 cytokines like IL-4 promote collagen formation and extracellular matrix deposition, which is intriguing to investigate the involvement of iNKT2 cells in SLD-induced fibrosis.[151]

γδ T cells are another type of innate-like T cell that exists in the steady-state liver and develops and is sustained in a microbiota-dependent way.[178] During SLD, the number of γδ T cells in the mouse liver rises, promoting hepatic damage. Importantly, the formation of hepatic γδ T cells is hindered in $Cd1d^{-/-}$ mice, which may contribute to the dampened SLD phenotype.[179]

MAIT cells proliferate during SLD development, and their absence exacerbates hepatic inflammation and damage.[180,181] However, it remains unclear how MAIT cells protect against diet-induced SLD, despite possessing pro-inflammatory characteristics similar to monocyte-derived macrophages and enhancing the mitogenic and pro-inflammatory functions of fibrogenic cells.[182] Additionally, this study did not investigate the involvement of MAIT cells in fi-

brosis, although previous studies have suggested a pro-fibrogenic impact of MAIT cells in acute liver injury models.[183] Therefore, further research is warranted to elucidate the role of MAIT cells in SLD, particularly in hepatic damage.

Platelets in SLD

In addition to their primary roles in coagulation and hemostasis, platelets also play a role in regulating inflammatory processes.[184] For example, platelets coming into contact with blood-borne pathogens enhance Kupffer cell-mediated bacterial clearance in the liver. Moreover, platelets collaborate with monocytes to promote atherosclerotic plaque formation, boost arterial inflammation and facilitate additional leukocyte recruitment.[185,186] Platelets are implicated in the development of SLD. Anti-platelet medication has been shown to reduce SLD development in mice.[187] However, the underlying processes remain unknown. Recent research has revealed platelet activation, adhesion, and platelet-derived granules are crucial in SLD development. Platelets interact with KCs during both the early and late phases of SLD, promoting steatosis, inflammation, and damage in mice. Additionally, platelets enhance the accumulation of inflammatory cells in the liver during SLD through a glycoprotein GPIbα-dependent mechanism.[188] Therefore, based on the aforementioned findings, platelets may play a significant role in SLD development.

Neutrophils in SLD

Compared to their positive effects in fighting infection, neutrophils exhibit a negative impact on chronic inflammatory diseases by producing ROS, cytokines, proteases, and neutrophil extracellular traps (NETs).[189,190] Both animal models and human biopsies demonstrate hepatic neutrophil infiltration in SLD.[191] Neutrophil accumulation occurs early in SLD mouse models.[192] Depleting neutrophils slows the progression of SLD in rats by reducing inflammation and liver damage, but these benefits diminish as the disease progresses. Inhibiting the serine protease neutrophil elastase has a similar effect in the early stages of SLD. Neutrophil elastase is produced as a component of NETs,[190] which are detected very early in the liver during

SLD pathogenesis in mice and at high levels in the blood of SLD patients.[193] Dismantling NETs using deoxyribonuclease I reduces hepatic inflammation, liver damage and liver fibrosis in rats, suggesting that these structures are harmful to SLD development.[193] Overall, neutrophils seem to play a crucial role in the initial stages of SLD through NETs formation, but their significance in later stages of SLD remains unknown.

Macrophages in SLD

Inflammatory signals during SLD promote the recruitment of blood monocytes to the liver, where they differentiate locally into monocyte-derived macrophages, expanding the liver's macrophage pool.[194] Recent research has given information on the variety of hepatic macrophages in SLD.[195]

A significant finding is that the self-maintenance of embryonically generated KCs is reduced in SLD mice due to the presence of KCs with low TIMD4 cell surface expression levels.[194] These TIMD4^{low} KCs resemble the monocyte-derived KCs that are produced in mice following the nonphysiological reduction of embryonically derived KCs, indicating the generation of monocyte-derived KCs during SLD.[196] Monocytes contribute to the pool of KCs during SLD, and immunostaining studies have shown that these monocyte-derived KCs localize to hepatic sinusoids, similar to embryonically formed KCs. Monocyte-derived KCs are generated in response to the increased mortality of embryonically derived KCs during SLD, with the goal of maintaining KCs levels. During SLD, a gene signature related to lipotoxicity is enriched in both embryonically generated and monocyte-derived KCs, as indicated by a transcriptomic study.

This type of cellular stress signature most likely explains why embryonically derived KCs die during SLD and why they are unable to effectively self-renew. Although the generation of KCs from monocytes helps maintain the KCs population in the liver, their gene expression profile differs from that of embryonically derived KCs. Specifically, monocyte-derived Kupffer cells do not exhibit the full spectrum of gene expression associated with auxiliary functions of embryonically derived KCs, such as erythrophagocytosis. As a result, monocyte-derived KCs have a more pronounced inflammatory profile compared to their embryonically derived counterparts.

Finally, monocyte-derived KCs and embryonically generated KCs have differing functional effects on SLD. Although monocyte-derived KCs reduce hepatic triglyceride accumulation, they cause more liver damage than embryonically produced KCs. Thus, during SLD, Kupffer cell homeostasis is significantly disrupted, which influences liver pathophysiology.[197]

Monocytes, in addition to contributing to the pool of KCs, follow a typical differentiation route during SLD, resulting in the formation of monocyte-derived inflammatory macrophages. It is worth noting that the SLD environment has a systemic influence on monocytes, as they already exhibit SLD-associated transcriptional changes in mouse bone marrow.[198] Monocyte-derived macrophages in the liver produce significant quantities of secreted phosphoprotein 1, integrin subunit alpha X, glycoprotein nonmetastatic B, CD9, and triggering receptor expressed on myeloid cells 2, all of which are also expressed in monocyte-derived KCs.[199] The monocyte-derived macrophages that accumulate in the liver during SLD resemble the lipid-associated macrophages found in obese white adipose tissue, suggesting that metabolic inflammation induces a common gene signature in monocyte-derived macrophages in different tissues and metabolic contexts.[200] In terms of function, monocyte-derived macrophages in the mouse liver localize to regions of tissue fibrosis near desmin$^+$ HSCs, indicating their potential involvement in hepatic fibrosis.[201] Similar findings were reported in cirrhotic human liver.[202] During human liver fibrosis, a TREM2$^+$CD9$^+$ monocyte-derived macrophage population with profibrotic characteristics increases.[202]

As previously stated, various immune cell populations are involved in SLD pathogenesis, and the roles of additional immune cell subsets, such as NK cells and ILCs, are still unknown. The hepatic inflammatory environment seen during SLD might result from coordinated immune cell interactions. Nevertheless, the detailed pathogenesis of SLD with this comprehensive immune response has not been extensively investigated.

In summary, various immune cells, including B cells, plasma cells, dendritic cells, conventional CD4+ and CD8+ T cells, innate-like T cells, platelets, neutrophils and macrophages play crucial roles in the development of MetALD and MASLD. Targeting the immune mechanisms of MetALD and MASLD holds significant therapeutic potential, and numerous clinical studies are required to investigate potential targeted therapies.

Immune cells in HCC

SLD is the primary risk factor for the development of HCC, due to alterations in the immune cell environment caused by liver inflammation as mentioned earlier.[203,204] In a mouse model of HFD-induced SLD and HCC, CD8$^+$ T cells and NKT cells contribute to hepatic steatosis and damage, ultimately resulting in the progression of SLD to HCC. Notably, the depletion of CD8$^+$ T cells and NKT cells does not worsen the advancement of SLD, which could serve as a foundation for preventing HCC development.[162]

In addition, CD8$^+$ T cells protect IgA-deficient MUP-uPA mice fed an HFD from SLD-induced HCC. CD8$^+$ T cells have a limited ability to promote the progression of SLD, as HCC resistance is associated with a decrease in depleted CD8$^+$ T cells. Subsequently, PDL1 blockade improved T cell dysfunction in MUP-uPA mice fed an HFD, resulting in enhanced anti-tumor immune function and reduced tumor incidence. Therefore, CD8$^+$ T cells play a crucial role in anti-tumor effects in HFD-fed MUP-uPA mice. Additionally, Cd8a-deficient mice exhibit a higher tumor burden in other SLD-induced HCC models. This study suggests that despite the high tumor burden, the improvement of SLD severity by CD8$^+$ T cells is limited, which may also contribute significantly to their anti-tumor effect. In summary, in other models, the role of CD8$^+$ T cells in promoting SLD pathogenesis may mask their superior anti-tumor ability.[205]

In the SLD-enhanced HCC mice model, CD4$^+$ T cells have been proven to inhibit the development of HCC. In this model, fatty acids induce CD4$^+$ T cell apoptosis through mitochondrial ROS production, while ROS clearance limits CD4$^+$ T cell loss and reduces tumor burden.[206] The impact of CD4$^+$ T cells on tumor growth is attributed to their ability to initiate tumor-specific immune responses, rather than their ability to contribute to the progression of MASH. Furthermore, in another SLD-enhanced HCC model, the opposite effect of CD4$^+$ T cells has been demonstrated. Additionally, T_H17 cells that produce IL-17A promote the development of SLD towards HCC through IL-17A-induced signaling in myeloid cells. In this study, T_H17 cells accelerate the progression of SLD disease rather than playing a role in anti-tumor immune responses, resulting in

a faster transition from SLD to HCC.[158,207] Therefore, depending on the model used for the transition from SLD to HCC, CD4$^+$ T cells can regulate the transition from SLD to HCC through different mechanisms.

Innate immune cells can also affect SLD induced HCC. Neutrophils accelerate the development of SLD by releasing NETs. Restricting the production of NETs reduces inflammatory factors related to SLD and inhibits SLD-induced HCC, where the reason is the limited development of SLD.[193] The mechanism of other myeloid cells such as KCs in SLD induced HCC has not been studied and still requires a lot of research to explore.

Innate immune cells can also influence SLD-induced HCC. Neutrophils accelerate the development of SLD by releasing NETs. Limiting the production of NETs decreases inflammatory factors associated with SLD and hinders SLD-induced HCC, as the restricted SLD development is the cause.[193] The role of other myeloid cells, such as KCs, in SLD-induced HCC has not been investigated and necessitates further research.

POTENTIAL THERAPEUTIC MODULATIONS

Targeting inflammatory responses

Chronic inflammation is a key factor in the development of MetALD and MASLD, indicating that regulating inflammatory response is a promising therapeutic strategy for improving disease progression in MetALD and MASLD (Table 2). Since many immune cells, including NK cells, neutrophils, and KCs, as well as inflammatory mediators, including TNF-α, TLR4 and IL-1β, play multiple functions in liver damage and regeneration, comprehensive treatment strategies are required rather than just promoting or inhibiting inflammatory responses.[208] Corticosteroids, such as prednisone, are now frequently utilized as first-line anti-inflammatory medications in patients with severe ASH. Prednisone, however, raises the risk of bacterial and fungal infections and is ineffective in the majority of patients.[209]

In MetALD, two randomized controlled trials with anti-TNF medications, such as enalapril and infliximab, display unsatisfactory results, and the anti-TNF group has a higher number of deaths in patients with severe ASH.[210,211] In MASLD, pentoxifylline (PTX) as a methylxanthine deriva-

tive inhibits several pro-inflammatory cytokines like TNF-α, which exhibits lipid peroxidation inhibition, oxidative stress reduction, and peroxyl and hydroxyl radical scavenging properties.[212,213]

The effects of anti-IL-1 on individuals with ASH are being studied in two current randomized clinical trials. In the first trial, patients with severe ASH are being treated with kanamycin monoclonal antibodies from the IL-1β antibody family to see if they are safe and effective. After 28 days of therapy, the primary outcome was histological improvement in liver biopsy ASH (NCT03775109). The other research (NCT04072822) primarily assesses the impact of anakinra as an IL-1 receptor antagonist on the 90-day death rate in individuals suffering from alcohol-associated hepatitis.[209]

TLR receptors are expressed on the surface of macrophages, dendritic cells and epithelial cells. The inflammation of MetALD may originate from initiating TLR response. In animal models, HA35, a tiny and specific-sized hyaluronic acid molecule, suppresses the ethanol-induced TLR4 signaling pathway in KCs.[214,215] A randomized controlled trial on the effects of HA35 on the change of skeletal muscle mass in patients with ASH is registered, but patient recruitment has not started (NCT05018481). TLR receptors is crucial for MASLD as well.[216] Long-acting JKB-121 is a tiny chemical that works well as a weak antagonist at the TLR4. It has recently been established that vitamin D is a hormone that has anti-inflammatory, antifibrotic, and immunomodulatory effects.[217] Well-designed studies have investigated the possibility that vitamin D alleviates MASH (NCT01623024).

Targeting bile acid dysregulation provides hepatoprotective effects by exerting anti-inflammatory and antioxidant effects and by regulating lipid metabolism. Drugs including farnesoid X receptor (FXR) agonists, peroxisome proliferator-activated receptor alpha (PPARα) agonists, ursodeoxycholic acid, and its derivatives have entered different phases of clinical trials, and some of them have shown promising therapeutic effects. For example, a phase II randomized clinical trial using obeticholic acid, an FXR agonist, in patients with ASH was conducted. However, the clinical trial is terminated because of hepatotoxicity associated with obeticholic acid (NCT02039219). Obeticholic acid as a steroidal FXR agonist improves fibrosis and key characteristics of MASLD in a phase III trial (NCT02548351).[218] However, it induces mild to moderate pruritus, HDL-C low-

Table 2. Immunological modulation in SLD pathogenesis

Modulation	Targeting/ Formula	Candidate	Diseases	Reference
Targeting hepatocyte death	Oxidative stress	N-acetylcysteine	MetALD	[222]
		Metoprolol	MetALD	[223]
		S-adenosylmethionine	MetALD	[224, 225]
		Selonsertib	MASLD	[226]
		Vitamin E	MASLD	[227, 228]
		Betaine	MASLD	[230]
		Ursodeoxycholic acid	MASLD	[231]
	Liver regeneration	G-CSF	MetALD	[232, 233]
		F-652	MetALD	[234]
		Bavachinin	MASLD	[235]
Targeting inflammatory responses	Inflammatory factor	Prednisone	MetALD	[209]
	TNF	Infliximab	MetALD	[210]
		Enalapril	MetALD	[211]
		PTX	MASLD	[213]
				[212]
	TLR	JKB-121	MASLD	[217]
		Vitamin D	MASLD	[217]
		HA35	MetALD	[214, 215]
	IL-1	Anakinra	MetALD	[209]
	FXR	Obeticholic acid	MetALD	NA
		Obeticholic acid	MASLD	[218]
		EDP-305	MASLD	[220]
	LPS	HA35	MetALD	[214]
		IMM-124E	MASLD	[221]
Targeting gut microbiota	*Lactobacillus rhamnosus* GG	Probiotics	MetALD	[238]
	Lactobacillus rhamnosus R0011 *and Lactobacillus acidophilus* R0052	Probiotics	MetALD	[239, 240]
	Streptococcus *thermophilus*, *Bifidobacterium* and *Lactobacillus*	Probiotics	MASLD	[244]
	Inulin-type fructans	Prebiotic	MASLD	[246]
	Oligofructose	Prebiotic	MASLD	[245]
	Vancomycin, gentamicin and meropenem	Antibiotics	MetALD	[241]
	Cidomycin	Antibiotics	MASLD	[247]
	Rifaximin	Antibiotics	MASLD	[248]
	Amoxicillin	Antibiotics	MetALD	[242]
	Lachnospiraceae and *Ruminococcaceae*	FMT	MetALD	[250]
	Healthy donor microbiome	FMT	MetALD	[251]
		FMT	MASLD	[252]

SLD, steatotic liver diseases; MetALD, metabolic dysfunction-associated alcoholic liver disease; TLR, toll-like receptors; IL, interleukin; FXR, farnesoid X receptor; LPS, lipopolysaccharide; FMT, fecal microbiota transplantation.

ering, LDL-C increasing, and a potential for drug-induced liver toxicity.[219] EDP-305, another potent steroidal FXR ag-

onist, is being developed. A phase IIa trial (NCT03421431) indicates that EDP-305 reduced ALT levels and liver fat

content. Its adverse events are the same as those of obeticholic acid, like pruritus, nausea, vomiting, diarrhea, headache and dizziness.[220]

Reducing LPS inhibits the activation of inflammatory cells and releases inflammatory mediators, which has a positive effect on improving MetALD. The ability of the antioxidant HA35 to reduce liver damage by preventing LPS from flowing out of the intestine has been demonstrated in animal models.[214] Oral administration of IMM-124E, an anti-LPS-enriched bovine colostrum, is suggested to alleviate chronic inflammation, liver damage, and insulin resistance associated with MASLD in mice models and a small cohort of patients with biopsy-proven MASLD.[221]

Targeting hepatocyte death

Hepatocyte injury plays an important role in the progression of MetALD and MASLD, and treatment for hepatocyte injury is considered promising therapies (Table 2). Long-term exposure to ethanol can lead to depletion of glutathione, making hepatocytes more susceptible to oxidative stress. Oxidative stress is one of the key mechanisms leading to hepatocyte damage in MetALD. Nevertheless, individual classic antioxidant molecules such as N-acetyl-cysteine or metoprolol are not effective against severe forms of ASH.[222,223] One of the reasons for the failure of these antioxidant therapies in ASH might be the absence of particular mitochondrial antioxidant effects. S-adenosyl-methionine may be a viable treatment option for MetALD, since this molecule can restore glutathione in mitochondria and ameliorate steatosis in animals.[224,225] More clinical trials are needed to determine the efficacy of mitochondrial-targeted antioxidants in treating ASH. However, there is currently a scarcity of therapeutic modulations that target these hepatocyte death patterns. Because of the link between several types of cell death and MetALD, blocking a single cell death mechanism may not be enough to ameliorate ASH. In a phase II clinical trial, selonsertib (GS-4997), an oral inhibitor of apoptosis signal regulated kinase-1 enzyme, has no advantages over prednisone alone in the treatment of severe ASH (NCT02854631).[226] Some clinical studies targeting apoptosis are increasing in MASLD. GS-4997 reduces liver fibrosis in the phase II trial. However, a phase III trial suggests that selonsertib had no anti-fibrotic effect in patients with bridging fibrosis or compensated cir-

rhosis due to MASLD.[227,228] Therefore, the anti-MASLD clinical research of GS-4997 is terminated. Antioxidants such as vitamin E, betaine and ursodeoxycholic acid show a better clinical perspective in MASLD.[229-231] For example, vitamin E alleviates MASLD progression as well as improved hepatic steatosis and lobular inflammation, but without effect on the development of fibrosis.[229]

It is difficult to inhibit hepatocyte mortality, thus encouraging liver regeneration is seen as a complementary therapeutic strategy. Granulocyte colony-stimulating factor (G-CSF) is a potent growth factor that accelerates liver cell regeneration in severe ASH. The meta-analysis results show that G-CSF is associated with a reduction of over 70% in mortality rate in ASH patients at 90 days.[232,233] In addition, IL-22 is a key anti-inflammatory cytokine that protects the liver and promotes regeneration. Currently, a phase II open-label clinical trial is now being conducted to investigate the impact of IL-22 agonists (F-652) on individuals with ASH. F-652 is a recombinant fusion protein containing human IL-22 and human IgG2 fragments, and its mechanism of action is identical to that of natural IL-22. Based on MELD and Lille scores, F-652 is associated with high improvement rates, increased liver regeneration markers and decreased inflammatory markers.[234] In MASLD, bavachinin is proven to possess liver-protecting effect against MAFLD, which binds to the pocket of PCNA facilitating its interaction with DNA polymerase delta and pro-regeneration effect.[235]

Targeting gut microbiota

In recent years, with the continuous improvement of understanding in the impact of intestinal pathophysiology, the gut microbiota has become the main target for studying the modulations of MetALD and MASLD (Table 2).[236,237]

Probiotics and antibiotics from early clinical studies have shown promising results in MetALD. For example, two ongoing randomized clinical trials are investigating the impact of probiotics on ASH patients. The first trial is currently being conducted to test the efficacy and safety of probiotics mainly *Lactobacillus rhamnosus* GG in patients with moderate ASH. The main endpoint is the change in MELD score after 30 days (NCT01922895).[238] Another study is evaluating the effects of probiotics mainly *Lactobacillus rhamnosus* R0011 and *Lactobacillus acidophilus* R0052

on liver enzyme, endotoxin, and cytokine levels in ASH patients after 7 days (NCT02335632).[239,240] Antibiotics also alter the gut microbiota. However, using a mixture of antibiotics such as vancomycin, gentamicin and meropenem, there was no improvement in hepatitis and systemic inflammation.[241] A multicenter, double-blind randomized controlled trial evaluated the efficacy of a combination of corticosteroids and antibiotic amoxicillin in the treatment of severe ASH (NCT02281929), and the results are yet to be confirmed.[242] At present, the role of conventional antibiotics in ASH management has not been determined.

Probiotics, prebiotics and antibiotic affect the gut microbiota in MASLD. VSL#3 as probiotic mixture is used for MASLD in clinical studies, which is a mixture of eight different bacteria such as *Bifidobacterium longum, Bifidobacterium infantis, Bifidobacterium breve, Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus plantarum, Lactobacillus casei* and *Streptococcus thermophilus*.[243] In a randomized controlled trial, the 4-month supplement of VSL#3 activated GLP-1, and improved fatty liver and body mass index in obese children with MASH (NCT01650025).[244] Prebiotics contain no living microorganisms and nondigestible food ingredients that selectively promote the proliferation of gut microbes. Oligofructose and inulin-type fructans as common prebiotics, increased the abundance of *Bifidobacterium spp*, and significantly improved hepatic steatosis and NAS (NCT03184376 and NCT03042494).[245,246] The treatment with cidomycin, as a non-absorbable antibiotic, indicates its potential to alleviating the severity of MASLD by intestinal microbiota modulations.[247] Besides, rifaximin as a non-absorbable, broad-spectrum and gastrointestinal-specific antibiotic displayed effective and safe in biopsy-proven MASH (NCT02884037 and EudraCT 2010-021515-17).[248]

Fecal microbiota transplantation (FMT) might be an option for rebuilding a healthy gut microbiota. In preliminary research and an open-label experiment, FMT in patients with severe ASH from healthy donors increased survival and liver function by reducing gut microbiota, which contributes to the development of ASH. These studies demonstrate that the donor microbiota can change the recipient microbiota and improve MetALD without complications, even in individuals with severe ASH.[249] Cytolysin-secreting E. faecalis strains are an important factor contributing significantly to hepatocyte damage and mortality in individuals with severe alcoholism. Individuals with alcoholism had much higher numbers of E. faecalis in their feces than non-alcoholics or individuals with alcohol-related illnesses. Interestingly, the overall quantity of E. faecalis, not just the presence of cytolysin-positive strains, may be important in the severity of liver disease and subsequent mortality.[250] In severe ASH, FMT improves 90-day survival and reduces infections by positively regulating microbial communities such as pathogenic taxa and anaerobes, making it a viable option to prednisolone treatment. Importantly, this approach provides a way to precisely edit the gut microbiota.[251]

Clinical investigations have revealed that FMT may have a therapeutic impact on MASLD. In a randomized clinical study, FMT successfully improved the therapeutic benefits on MASLD patients, and its clinical efficacy was greater in lean MASLD patients than in obese MASLD patients.[252] The changes in gut microbiota composition caused by FMT further lead to plasma metabolites such as phenylacetyl-carnitine in MASLD patients' extensive changes in phenylacetylcarnitine, phenylacetylglutamine and choline-derived metabolites and liver DNA methylation profiles.[253] Notably, other clinical trials evaluating the treatment of MASLD patients with FMT are presently underway (NCT02469272).

PERSPECTIVES

SLD are important chronic liver disorders that affect people worldwide, and their pathogens involve multiple mechanisms. Immunity plays a crucial role in promoting the progression from SLD to more severe forms of liver injury, such as steatohepatitis, cirrhosis and HCC. Immunity involves multiple mechanisms in the progression of SLD, mainly affecting intestinal disorders, the adipose-liver axis, accelerating hepatocyte death and affecting immune cell-mediated inflammatory processes. Additionally, multiple immune cells are involved, including B cells, plasma cells, dendritic cells, conventional CD4+ and CD8+ T cells, innate-like T cells, platelets, neutrophils and macrophages. Some immunological modulations targeting hepatocyte death, inflammatory responses and gut microbiome are constantly increasing. The immunological modulations mainly include N-acetylcysteine, selonsertib, F-652, prednisone, pentoxifylline, anakinra, JKB-121, HA35, obeticholic acid, probiot-

ics, prebiotics, antibiotics and FMT. However, our understanding of the immunological signals that drive SLD is incomplete, and further research is needed to better understand the involvement of specific immune cell subsets in these diseases. Future research to identify these key immunity drivers will not only enhance our understanding of the etiology of SLD but also discover new effective therapeutic interventions for treating MetALD and MASLD. We look forward to more clinical trials targeting immunological mechanisms for SLD in the future.

Authors' contribution

Mengyao Yan: Investigation, writing original draft, review & editing, figure drawing. Shuli Man: Conceptualization, design, writing-review & editing, figure drawing, funding acquisition. Long Ma: Supervision, review & editing. Lanping Guo and Luqi Huang: Review & editing. Wenyuan Gao: Conceptualization, review & editing. The final version of the work has been read and approved by all of the authors.

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Conflicts of Interest

The authors declare that there are no conflicts of interest

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