World Journal of Diabetes

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World J Diabetes 2025 September 15; 16(9): 110515

DOI: 10.4239/wjd.v16.i9.110515

ISSN 1948-9358 (online)

REVIEW

Macrophage and inflammation in diabetes and metabolic dysfunction-associated steatotic liver disease: From mechanisms to therapeutic strategies

Chun-Ye Zhang, Shuai Liu, Ming Yang

Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade A, Grade B, Grade C

Novelty: Grade A, Grade A, Grade E

Creativity or Innovation: Grade A, Grade A, Grade E

Scientific Significance: Grade A, Grade A, Grade D

P-Reviewer: Islam S, PhD, Professor, South Africa; Kumar A, Research Fellow, India; Li N, PhD, Research Assistant Professor, China

Received: June 9, 2025

Revised: July 8, 2025

Accepted: August 26, 2025

Published online: September 15, 2025

Processing time: 95 Days and 18.6 Hours

Chun-Ye Zhang, Bond Life Sciences Center, University of Missouri, Columbia, MO 65212, United States

Shuai Liu, The First Affiliated Hospital, Zhejiang University, Hangzhou 310006, Zhejiang Province, China

Ming Yang, Department of Surgery, University of Connecticut, School of Medicine, Farmington, CT 06030, United States

Corresponding author: Ming Yang, PhD, Assistant Professor, Department of Surgery, University of Connecticut, School of Medicine, 263 Farmington Avenue, Farmington, CT 06030, United States. minyang@uchc.edu

Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is featured by the accumulation of excessive fat in the liver. It is caused by many factors, such as overweight, obesity, diabetes, and high plasma levels of sugar, cholesterol, and triglycerides. MASLD is commonly associated with type 2 diabetes (T2D), which is characterized by a pathophysiological deficiency of insulin secretion due to impaired function of pancreatic β cells and insulin resistance. T2D has become a global pandemic that influences more than 21.7 million people worldwide. Preclinical and clinical studies have been performed to investigate molecular crosslinks between T2D and MASLD and their therapeutic strategies. Accumulating evidence has demonstrated that macrophages are cellular mediators that contribute to the progression of MASLD and T2D by impacting the resolution of inflammation. Different types of macrophages are involved in the pathogenesis of MASLD and T2D, including liver-resident macrophages or Kupffer cells, monocyte-derived macrophages, and adipose tissue macrophages. These macrophages secrete enzymes, chemokines, cytokines, as well as exosomes, to induce metabolic inflammation and insulin resistance, immune cell infiltration, and tissue injury. In this review, we provide a comprehensive summary of the molecular and cellular interactions between MASLD and T2D with a specific discussion of the critical roles of macrophages and inflammation. The underlying molecular mechanisms and the associated therapeutic targets and strategies are also reviewed.

Key Words: Macrophage; Inflammation; Diabetes; Metabolic dysfunction-associated

steatotic liver disease; Mechanism; Cytokines; Therapy

Core Tip: Macrophages are an important cellular component that regulates metabolic disorders, including metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes (T2D). Macrophage-derived cytokines, chemokines, and metabolic products contribute to metabolic inflammation and insulin resistance, immune cell infiltration, and tissue injury. The phenotype and function of macrophages are important factors for evaluating the efficacy of MASLD and T2D treatments. Clinical trials are ongoing to dissect the roles of macrophages and test macrophage-targeted therapies in MASLD, T2D, and other related metabolic disorders.

Citation: Zhang CY, Liu S, Yang M. Macrophage and inflammation in diabetes and metabolic dysfunction-associated steatotic liver disease: From mechanisms to therapeutic strategies. *World J Diabetes* 2025; 16(9): 110515
URL: https://www.wjgnet.com/1948-9358/full/v16/i9/110515.htm
DOI: https://dx.doi.org/10.4239/wjd.v16.i9.110515

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), (previously known as non-alcoholic fatty liver disease or NAFLD) is characterized by the accumulation of excessive fat in the liver[1]. Many factors, such as overweight, obesity, diabetes, and high levels of plasma sugar, cholesterol, and triglycerides, contribute to MASLD development. Metabolic dysfunction-associated steatohepatitis (MASH) is an advanced stage of MASLD with the progression of liver inflammation, cell death, and various liver fibrosis. The progression of MASLD or MASH could increase the risk of liver cirrhosis and primary liver cancer, with a predominant type of hepatocellular carcinoma[2]. MASLD is a rapidly growing health concern, affecting more than a quarter of the global population[3]. Type 2 diabetes (T2D) is closely associated with MASLD, and approximately 60%-70% of T2D patients have MASLD[4]. T2D is characterized by the pathophysiological deficiency of insulin secretion due to impaired function of the pancreatic islet β-cells and the occurrence of insulin resistance. T2D has become a global pandemic and influences more than 21.7 million people worldwide[5]. Given the high co-occurrence of MASLD and T2D, it is necessary to investigate the underlying molecular and cellular crosslinks between MASLD and T2D[6], which can provide the foundation for developing therapeutic targets and treatment strategies for MASLD and T2D.

Macrophages play a crucial role in host health and disease through immune surveillance[7]. They are responsible for detecting the pathogen-related molecules or damage-related molecules and clearing pathogens and dead cell components by phagocytosis[8]. Tissue resident macrophages maintain local tissue homeostasis[9]. Accumulating data show that macrophages, such as adipose tissue macrophages and liver-resident macrophages consisting of Kupffer cells and monocyte-derived macrophages, function as important mediators in the cellular mechanisms in both MASLD and T2D [10,11]. Meanwhile, inflammation plays a pivotal role in both MASLD and T2D. Notably, macrophage-mediated inflammation is essential in metabolic disorders[12,13]. Therefore, in this review, we focus on the function of macrophages and inflammation and summarize the cellular and molecular mechanisms mediating the crosslinking between MASLD and T2D. In addition, the related therapeutic targets, treatment strategies, and clinical trials are summarized.

MACROPHAGES IN GENERAL

Macrophages are immune cells that play essential roles in host immune defense through sensing, engulfing, and digesting pathogens or dead cell components. In addition, macrophages mediate inflammation by secreting molecules, such as cytokines and chemokines, and maintain tissue homeostasis by regulating tissue remodeling and repair[14]. Macrophages also play a pivotal role in metabolic regulation. Upon different stimulation, macrophages can be polarized into two different phenotypes, M1 and M2 polarization, which possess distinct functionality[15]. Classically activated M1 macrophages show proinflammatory function due to the production of proinflammatory molecules such as interleukin (IL)-6, IL-12, and tumor necrosis factor (TNF). In contrast, alternatively active M2 macrophages own anti-inflammatory function, which is characterized by the release of anti-inflammatory molecules, such as IL-10 and transforming growth factor beta (TGF-β)[8]. The ratio or balance of M1 and M2 is critical in maintaining tissue homeostasis and inflammatory status[16].

Tissue-resident macrophages refer to the macrophages that are specifically located in different tissues, characterized by their heterogeneity depending on the tissue types in which they reside. Liver-resident macrophages, consisting of Kupffer cells and monocyte-derived macrophages, and adipose tissue macrophages, play a pivotal role in the progression of MASLD and T2D[17,18]. In the following sections, we will dissect the roles of these macrophages.

LIVER-RESIDENT MACROPHAGES IN MASLD AND T2D

Kupffer cells and monocyte-derived macrophages are cellular inflammatory regulators in MASLD and T2D, which reciprocally interact with each other to impact disease progression[19,20]. A proinflammatory condition increases the risk of T2D development and progression in patients. Mechanistically, Kupffer cells and monocyte-derived macrophages are differentiated into M1 macrophages to exacerbate an inflammatory response *via* the secretion of cytokines and chemokines[21,22].

Kupffer cells

Kupffer cells are originally derived from erythromyeloid progenitors of the yolk sac[23]. They can be polarized into M1 phenotype by cytokines, such as IL-1β, IL-6, IL-12, interferon-gamma (IFN-γ), TNF-α, and lipopolysaccharide (LPS). These activated Kupffer cells can subsequently trigger the proinflammatory response to induce tissue inflammation and damage[24,25]. A recent study revealed that CCAAT/enhancer binding protein beta (C/EBPβ) was overexpressed in Kupffer cells in a high-fat and high-cholesterol diet-induced mouse MASLD model. C/EBPβ is a transcription factor that contributes to inflammation, metabolic dysfunction, and immune dysregulation. Metabolic abnormality induced the upregulation of C/EBPβ in the liver tissues of MASLD subjects. The elevated level of C/EBPβ further increased the expression of vascular cell adhesion protein 1 in Kupffer cells, which exacerbated hepatic immune cell infiltration and liver inflammation[26]. Interestingly, C/EBPβ is known to contribute to the pathological progression of T2D, which is associated with pancreatic β-cell dysfunction and insulin secretion reduction[27]. Meanwhile, C/EBPβ also plays a significant role in the peroxisome proliferator-activated receptors signaling pathway, a well-known pathway involved in both MASLD and T2D[28].

Monocyte-derived macrophages

Blood circulating monocytes, which originated from hematopoietic stem cells, can differentiate into M1 macrophages upon the cytokine stimulation of granulocyte-macrophage colony-stimulating factor along with IFN-γ and LPS[29,30]. This process results in the formation of monocyte-derived M1 macrophages, which can secrete lots of proinflammatory cytokines, including IL-1α, IL-1β, IL-6, IL-12, TNF-α, IL-23, CXCL9, CXCL10, CXCL11, CXCL16 and CCL5. Overexpression of these cytokines and chemokines can cause inflammation and tissue damage[31,32].

Monocyte-derived macrophages also play an essential role in MASLD and T2D. A recent study focused on the Glycoprotein non-metastatic melanoma protein b (GPNMB), encoded by the gene *Gpnmb*. GPNMB is a lipid-associated macrophage marker[33,34]. It is a transmembrane glycoprotein, which is predominantly expressed in hepatic monocyte-derived macrophages and white adipose tissues[35]. Numerous studies have demonstrated that there is an upregulation of *Gpnmb* expression in MASLD livers[36]. A recent study using a myeloid-specific *Gpnmb*-knockout mouse model discovered that knockout of *Gpnmb* maintained the population of Kupffer cells and reduced liver steatosis and fibrosis. This study also revealed that myeloid-specific knockout of *Gpnmb* directed monocyte differentiation towards a monocyte-derived macrophage subset rather than lipid-associated macrophages, which can exacerbate the severity of MASLD[33,37]. In a fructose-palmitate-cholesterol diet-induced mouse MASLD model, knockdown of *Gpnmb* showed a protective effect by ameliorating liver steatosis and hepatitis. The underlying mechanism is that knockdown of *Gpnmb* increased the expression levels of activin A to protect against liver injury in MASLD[36]. Interestingly, T2D patients also exhibit elevated levels of serum GPNMB, which are associated with the progression of insulin resistance[35,38]. Another study showed that an increased ratio of monocytes to apolipoprotein A1 predicted a higher risk of MASLD in patients with T2D [39]. This further highlights the monocyte-derived macrophages in the correlation and connection between MASLD and T2D.

Liver resident macrophages serve as a link between MASLD and T2D

Liver resident macrophages, including both Kupffer cells and monocyte-derived macrophages, are considered to function as a great contributor in linking MASLD and T2D. In disease conditions, MASLD and T2D, the liver resident macrophages are involved in the processes of inflammation, insulin resistance, fibrogenesis, and lipid metabolism, and all these factors contribute to the linkage of these two diseases (Figure 1). Polarized M1 Kupffer cells or monocyte-derived macrophages contribute to the inflammation by secreting proinflammatory cytokines and chemokines (Table 1), such as TNF-α, ILs, CXCLs, and CCLs[40-42]. Inflammation and tissue damage further exacerbate and worsen the pathological condition to accelerate the development of metabolic disorders. Besides inflammation, MASLD and T2D-induced insulin resistance can promote hyperlipidemia, hyperglycemia, glucotoxicity, and lipotoxicity[43-46]. Those dysfunctions may further induce endoplasmic reticulum (ER) stress, inflammation, free fatty acid (FFA) level, fibrosis, oxidative stress, and mitochondrial dysfunction, contributing to MASLD progression and beta cell defect[47-49].

ADIPOSE TISSUE MACROPHAGES IN MASLD AND T2D

In MASLD or T2D, a large number of macrophages infiltrate into adipose tissues, followed by their polarization[50-52], with an increase of M1 macrophages and a decrease of M2 macrophages (Figure 2). The activation of nuclear factor kappa-light-chain-enhancer of activated B cells of M1 macrophages promotes the secretion of proinflammatory cytokines, such as TNF-α, IL-6, IL-12, and IL-1β, consequently decreasing the phagocytosis function[53]. Proinflammatory environment exacerbates the pathogenesis of MASLD and T2D in a bidirectional way. Meanwhile, pro-inflammation reciprocally aggravates the insulin resistance to worsen T2D and MASLD[54,55]. Moreover, adipose tissue macrophages

Table 1 Macrophage-derived mediators in metabolic dysfunction-associated steatotic liver disease and type 2 diabetes

Mediators	Sources	Function in T2D	Function in MASLD
IL-1α	Kupffer cells and recruited monocyte-derived macrophages	Promote inflammation and worsen insulin resistance and metabolic syndrome	Contribute to hepatic steatosis, inflammatory cell recruitment, fibrosis progression, and systemic insulin resistance
IL-1β	Adipose tissue macrophages and Kupffer cells	Promote β-cell inflammation and ER stress, induce β-cell apoptosis, and impair glucose-stimulated insulin secretion	Exacerbate liver inflammation and MASLD development and promote the progression from steatosis to steatohepatitis
IL-6	Adipose tissue macrophages, Kupffer cells	Contribute to systemic insulin resistance and modulate adipocyte metabolism	Promote inflammation in MASLD and hepatic acute-phase response
IL-12	Adipose tissue macrophages and Kupffer cells	Reduce glucose infusion rates and impair insulin sensitivity	Boost hepatic inflammation and insulin resistance in MASLD
IL-23	Adipose tissue macrophages and Kupffer cells	Contribute to IL-17/IL-23 axis-mediated inflammatory responses and induce metabolic stress	Promote pro-inflammatory responses mediated by IL-17/IL-23 axis and induce metabolic stress
TNF-α	Adipose tissue macrophages and Kupffer cells	Promote insulin resistance *via* insulin receptor substrate 1 serine phosphorylation, exacerbate β-cell dysfunction and apoptosis, and induce lipolysis	Promotes hepatocyte apoptosis, fibrosis, and inflammation in MASLD, and contribute to meta-inflammation and systemic inflammation
IL-10	M2 macrophages (alternatively activated)	Promote tissue repair and protect against insulin resistance	Promote tissue repair and reduce inflammatory progression and fibrosis in MASLD
CCL2 (MCP-1)	Macrophages, adipose tissue macrophages	Promote recruitment of circulating monocytes to adipose tissue, promote macrophage infiltration and inflammation, and exacerbate insulin resistance	Recruit circulating monocytes to adipose tissue, perpetuate macrophage infiltration and inflammation, promote hepatic macrophage accumulation and fibrosis
CCL5	Macrophages	Induce chronic inflammation in T2D	Promote MASLD and liver fibrosis progression
CXCL9	Adipose tissue macrophages and Kupffer cells	Induce chronic inflammation in adipose tissue, stimulate inflammatory cytokine production, exacerbate insulin resistance, and induce tissue damage	Exacerbate liver inflammation and fibrosis, and augment systemic insulin resistance
CXCL10	Adipose tissue macrophages, Kupffer cells, and monocyte-derived macrophages	Promote metabolic inflammation and impaired insulin signaling, contribute to systemic and local inflammation, and exacerbate insulin resistance	Promote M1 macrophage polarization and recruitment, boost chronic inflammation in MASLD, and exacerbate insulin resistance
CXCL11	Adipose tissue macrophages, adipose tissue macrophages, Kupffer cells, and monocyte-derived macrophages	Exacerbate insulin resistance and influence systemic metabolism	Boost inflammatory and fibrotic progression in MASLD/MASH and promote insulin resistance and metabolic dysregulation
CXCL16	Adipose tissue macrophages, Kupffer cells, and recruited monocyte-derived macrophages	Induce chronic inflammation and metabolic dysfunction and contribute to insulin resistance in T2D	Increase macrophage infiltration, stimulate inflammatory cytokine secretion (*e.g.*, TNF-α), influence hepatocyte metabolism and stellate cell collagen production, and increase steatohepatitis severity and fibrosis progression

T2D: Type 2 diabetes; MASLD: Metabolic dysfunction-associated steatotic liver disease; IL: Interleukin; TNF: Tumor necrosis factor; MCP-1: Monocyte chemoattractant protein-1; MASH: Metabolic dysfunction-associated steatohepatitis.

could accelerate glucose production and increase insulin resistance to promote MASLD, which in turn drives adipose tissue macrophage recruitment and polarization. Adipose tissue macrophage recruitment and polarization can decrease insulin secretion to promote the development of T2D[56].

Adipose tissue macrophage serves a critical role in the linkage between MASLD and T2D. The underlying mechanisms of this crosstalk include inflammation, insulin resistance, insulin tissue impairment, fibrogenesis, and metabolic dysfunction[11,57]. In MASLD, fat accumulation causes chronic inflammation in adipose tissue[58]. Since macrophages are the most abundant immune cells in inflamed adipose tissues, and they predominantly differentiate into proinflammatory M1 type, these macrophages serve as a great contributor to tissue inflammation and dysregulation of the insulin-related signaling pathways[59]. These conditions can promote insulin resistance to induce the development of T2D. Insulin tissue impairment can further induce fat metabolic dysregulation, FFA production, and lipotoxicity, which confer an unfavorable condition for both MASLD and T2D[60,61].

A recent clinical trial performed in participants diagnosed with both MASLD and T2D demonstrated the synergistic therapeutic effect by combining the insulin-sensitizer pioglitazone and glucose control medicine empagliflozin. Empagliflozin was reported to have a weight control effect. The results showed the treatment had a significant beneficial effect in alleviating MASLD, decreasing visceral fat, and increasing the levels of adiponectin in T2D patients. Notably, adiponectin is mainly produced by adipose tissues and serves as a regulator for fat metabolism, such as glucose and fatty acids[62]. This study not only underlines the important connection between MASLD and T2D, but it also highlights the

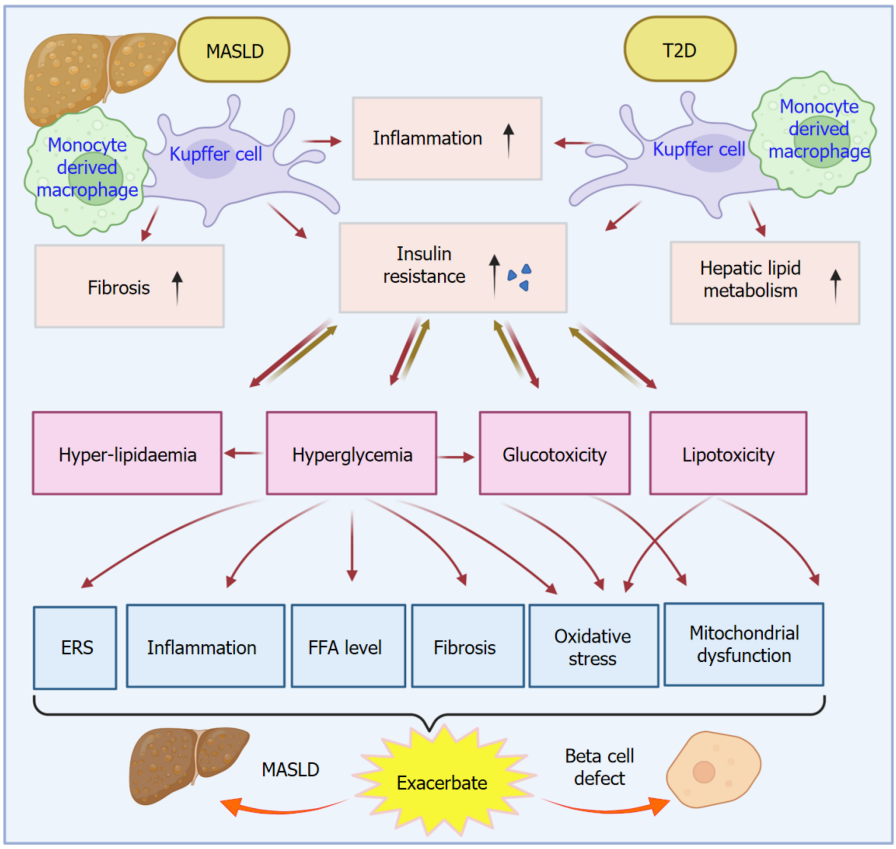

Figure 1 Liver resident macrophage, Kupffer cells, and monocyte-derived macrophages play an essential role in the crosslink of metabolic dysfunction-associated steatotic liver disease and type 2 diabetes. Liver macrophages, including both liver-resident Kupffer cells and monocyte-derived macrophages, serve as a cellular link between metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes (T2D) through a variety of factors such as inflammation, insulin resistance, fibrosis, and hepatic lipid metabolism. The increased insulin resistance resulting from MASLD and T2D leads to hyperlipidemia, hyperglycemia, glucotoxicity, and lipotoxicity. These factors subsequently exacerbate the MASLD and beta cell defect by increasing endoplasmic reticulum stress, oxidative stress, inflammation, increased free fatty acid level, fibrosis, and mitochondrial dysfunction. T2D: Type 2 diabetes; MASLD: Metabolic dysfunction-associated steatotic liver disease; ERS: Endoplasmic reticulum stress; FFA: Free fatty acid.

key role of the reduction of adipose tissue-related inflammation and insulin resistance in MASLD and T2D therapy.

Polarized adipose tissue M1 macrophages contribute to fibrogenesis in adipose tissues. In MASLD and/or T2D, polarized adipose tissue M1 macrophages induced by proinflammatory response can secrete pro-fibrotic cytokines, such as TNF-α, TGF-β1, IL-1β, IL-6, IL-13, and platelet-derived growth factor, to induce the activation of fibroblasts and consequently cause tissue damage and fibrosis[63]. Activated fibroblasts produce more collagen to induce the accumulation of extracellular matrix (ECM) components and fibrosis[64,65]. On the other hand, the reduced collagen degradation of macrophages also contributes to the failure of ECM clearance and ECM deposition. Moreover, preadipocytes interact with proinflammatory M1 macrophages to increase the formation of ECM, including collagen 1 and fibronectin. Fibronectins promote cell adhesion, migration, and tissue remodeling, causing various pathologic processes[66].

It has been reported that in patients with MASLD, the degree of hepatic fibrosis was correlated with the amount of proinflammatory adipose tissue macrophages, and the progression of liver fibrosis could be ameliorated by modulating adipose tissue macrophages in a MASH model. In T2D, treatment with bromocriptine, an inhibitor of *CREBZF* in macrophages, improved adipose tissue macrophage activation, alleviated systemic insulin resistance, and attenuated the symptoms of T2D. The associated mechanism was contributed by the crosstalk between adipose tissue macrophages and adipocytes[67]. The deficiency of *CREBZF* in macrophages reduced macrophage infiltration in adipose tissues, hyperglycemia, and proinflammatory response in an insulin-resistant mouse model. This study underscores the important role of adipose tissue macrophages in regulating insulin resistance, inflammation, and energy metabolism in T2D and MASLD[68].

METABOLISM LINKAGE IN MASLD AND T2D

MASLD pathogenesis is featured by elevated levels of many factors, such as glucose, FFA, very-low-density lipoprotein (VLDL), cholesterol, C-reactive protein, coagulation factors, and fibrinogen (Figure 3). Those factors result from MASLD and reciprocally contribute to the exacerbation of MASLD and T2D pathogenesis[69-71]. Overexpression or an increase in these factors can induce β-cell dysfunction and insulin resistance, promoting the progression of T2D. The insulin

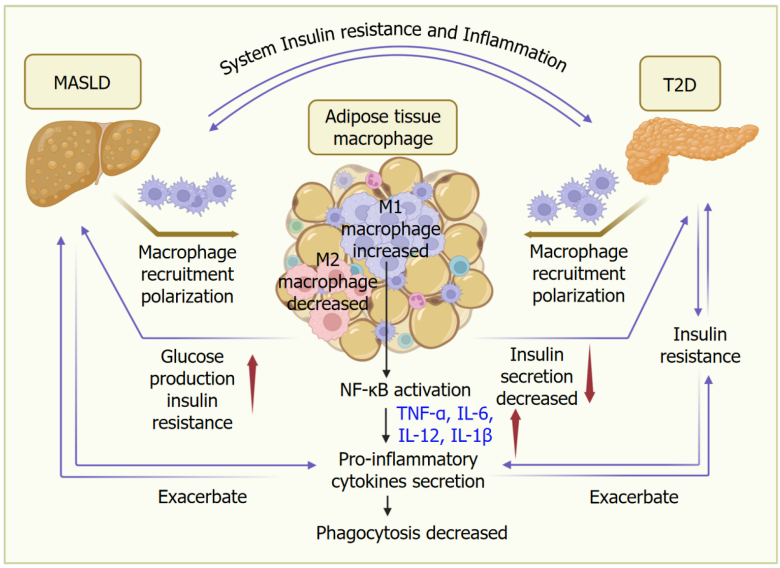

Figure 2 Adipose tissue macrophages play an essential role in the crosslink between metabolic dysfunction-associated steatotic liver disease and type 2 diabetes. Adipose tissue macrophages play an essential role in connecting metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes (T2D). MASLD and T2D promote the recruitment and polarization of macrophages in adipose tissues. Upon polarization and activation of nuclear factor kappa-B, M1 macrophages increase the expression of proinflammatory cytokines, such as tumor necrosis factor-α, interleukin (IL)-12, IL-6, and IL-1β, which results in a decreased phagocytosis function of macrophages. Proinflammatory response in adipose tissues further exacerbates insulin resistance to promote T2D and MASLD development. Adipose tissue macrophages also contribute to the aggregation of T2D and MASLD by increasing glucose production and insulin resistance, as well as reducing insulin secretion. Through systemic inflammation and insulin resistance, MASLD and T2D interact with each other in a bidirectional way. T2D: Type 2 diabetes; MASLD: Metabolic dysfunction-associated steatotic liver disease; NF-κB: Nuclear factor kappa-B; IL: Interleukin; TNF: Tumor necrosis factor.

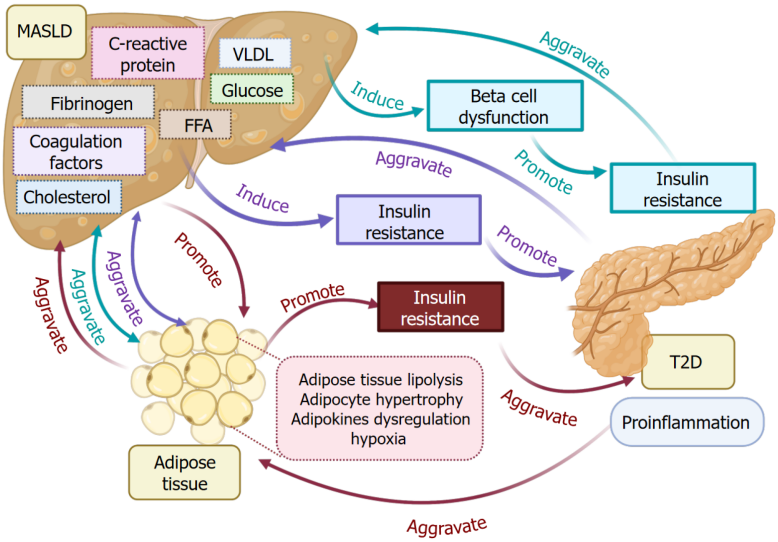

Figure 3 Metabolism function crosslinks among metabolic dysfunction-associated steatotic liver disease, type 2 diabetes, and adipose tissues. Metabolic disorder induces alterations of energy metabolism, such as elevated levels of glucose, free fatty acid, very-low-density lipoprotein and cholesterol, C-reactive protein, coagulation factors, and fibrinogen in metabolic dysfunction-associated steatotic liver disease (MASLD) livers, beta cell dysfunction, and insulin resistance, causing type 2 diabetes (T2D) progression. T2D aggravates MASLD reciprocally. Meanwhile, the elevated metabolic factors also promote adipose tissue lipolysis, adipocyte hypertrophy, adipokine dysregulation, and hypoxia, which promote insulin resistance and aggregate MASLD. T2D-associated insulin resistance and inflammation aggravate adipose tissue metabolic dysfunction. T2D: Type 2 diabetes; MASLD: Metabolic dysfunction-associated steatotic liver disease; FFA: Free fatty acid; VLDL: Very-low-density lipoprotein.

resistance in T2D further aggravates the development of MASLD. MASLD interacts with T2D through adipose tissues. Adipose tissue metabolism dysfunction in MASLD causes adipose tissue proinflammation and lipolysis, adipocyte hypertrophy, adipokine dysregulation, and hypoxia[72-74]. Those mentioned processes resulting from MASLD and T2D also contribute to their progression. Consequently, those processes further promote insulin resistance and aggravate T2D and inflammation.

Glucose

Glucose uptake from blood and storage as glycogen are essential physiological processes for maintaining a normal blood glucose level in healthy conditions. In this physiological process, insulin plays a pivotal role in sensing and signaling to initiate the process. However, in MASLD and T2D, the insulin resistance could decrease this process, resulting in an increased level of blood glucose, or hyperglycemia. Meanwhile, glucose and fructose can be metabolized into fatty acids through the *de novo* lipogenesis (DNL) pathway, followed by the incorporation of triglycerides[75,76]. Triglycerides are the main components of body fat. Notably, in MASLD and T2D, this process continues to promote excessive fat production and accumulation, which in turn worsens insulin resistance. Glucose production is controlled by insulin in healthy conditions. However, in pathological conditions, such as MASLD and T2D, insulin resistance can impair insulin suppression function, causing an increase in glucose production, known as glucogenesis. Glucogenesis can induce an increased level of glucose production and an elevated level of blood glucose, which leads to the aggravation of hyperglycemia[77,78].

Glucose dysregulation, its associated insulin resistance, and lipid dysregulation contribute to the flow of carbohydrate disruption *via* the pathway of glycolysis, DNL, and gluconeogenesis. Moreover, mitochondrial dysfunction and fatty acid oxidation induce overexpression of reactive oxygen species (ROS) and oxidative stress, which ultimately cause tissue injury. It has been reported that glucose-lowering drugs, such as sodium-glucose cotransporter-2 inhibitors, displayed beneficial treatment effects on decreasing hepatic fat, alleviating histological features, and alleviating liver cirrhosis in patients with MASLD and T2D[79,80].

FFA

Imbalance of FFA metabolism is highly associated with the development of MASLD. In both MASLD and T2D, an increased level of FFA contributes to the metabolic dysregulation and oxidative stress, consequently inducing β-cell dysfunction to promote the progression of T2D and MASLD[81,82]. Increased levels of FFA can cause lipotoxicity, consequently leading to oxidative stress, ER stress, inflammation, autophagy, and lipid apoptosis. All those factors contribute to the progression of MASLD[47,83].

Adipose tissue-released FFAs, originating from adipose tissue lipolysis, are taken by the liver, and then involved in the processes of lipogenesis, DNL, lipolysis, VLDL-related triglyceride secretion, and fatty acid β-oxidation[84,85]. An increase of FFA uptake, lipogenesis, and DNL, and a decrease of lipolysis, VLDL-related triglyceride secretion, and β-oxidation, can induce FFA metabolism imbalance and lead to the development of MASLD. Moreover, higher levels of FFAs worsen the MASLD and T2D by elevating insulin resistance.

According to a study conducted on enrolled patients, including a large population of the MASLD group and the non-MASLD group, the results showed that a higher level of FFAs was significantly associated with insulin resistance, prediabetes, and T2D in the group of MASLD, but not in the non-MASLD group. This result provides insight into the value of managing the level of FFAs in MASLD patients to monitor the risk of T2D development[60].

VLDL and cholesterol

VLDL is responsible for transporting triglycerides from the liver to different tissues through the vascular system. Upon the dislocation of triglycerides by enzymes, VLDL converts into low-density lipoprotein, which is considered unfavorable cholesterol. A high level of VLDL is a contributing factor to the development of metabolic syndrome and fatty liver[86]. In MASLD, an increased level of VLDL secretion in the liver, as well as in blood bloodstream, contributes to insulin resistance and dyslipidemia[87]. In T2D patients, an increased level of VLDL and triglycerides results from VLDL metabolic dysregulation and insulin resistance[88]. According to a recently published report, the excess triglycerides in VLDL or triglyceride-rich VLDL could be a useful biomarker for predicting MASLD in patients with T2D[89]. Another study reported that the ratio of triglyceride to high-density lipoprotein cholesterol can be applied to predict T2D in patients with MASLD[69].

The accumulation of cholesterol influences mitochondrial function. Mitochondria are responsible for the tricarboxylic acid cycle, fatty acid oxidation, energy metabolism, and thermogenesis. In addition, adipose tissue produces lipids, adipokines, cytokines, and chemokines induce oxidative stress, ER stress in MASLD livers, causing mitochondrial dysfunction and subsequently triggering ROS production. This process can induce mitochondrial oxidative damage, thereby resulting in severe metabolic dysfunction that otherwise could be well-maintained by mitochondria under normal conditions[90,91]. A recent study focused on targeting mitochondrial energy metabolism using HU6, a mitochondrial uncoupler, to treat individuals with MASLD and high body mass index (BMI) (28-45 kg/m^2). The clinical trial results showed that at least a 30% reduction in liver fat was observed when compared to baseline on day 61 in patients with MASLD and a high BMI[92]. Another study showed that salsalate, a non-steroidal anti-inflammatory drug, uncoupled mitochondria to demonstrate the function in alleviating metabolic disorders such as MASLD through adenosine 5′-monophosphate-activated protein kinase (AMPK) signaling pathway[93]. Thus, targeting mitochondria to manage the MASLD and T2D has gained extensive attention[94].

C-reactive protein

C-reactive protein is produced in the liver and is responsible for inflammation. An increased level of C-reactive protein is a common feature in both MASLD and T2D[95]. In hepatocytes, leptin regulates lipid metabolism to maintain energy balance and metabolic health. However, an increased C-reactive protein can disturb leptin regulatory function to cause lipid accumulation. This process leads to ROS production, followed by mitochondrial DNA production[96]. On the other hand, the released mitochondrial DNA triggered the activation of Toll-like receptors in the Kupffer cells and promoted the secretion of IL-6 and IL-1β. Meanwhile, accumulated lipids interacted with FFA receptors on the surface of Kupffer

cells and induced ROS production, which further facilitated the release of inflammatory cytokines. This process was mediated by the activation of nuclear factor kappa-B signaling pathway *via* the mitogen-activated protein kinase/extracellular signal-regulated kinase and AMPK/mammalian target of rapamycin (AMPK/mTOR) signaling pathways [97-99].

Coagulation factor fibrinogen

Fibrinogen, coagulation factor I, is produced by the liver and distributed to the bloodstream[100]. Upon the injury, it can be converted into fibrin and is responsible for stopping bleeding. In both MASLD and T2D patients, the level of fibrinogen is increased[101,102]. The elevated level of fibrinogen can induce the excessive production of fibrin in the liver and adipose tissues, which worsens the condition of inflammation and injury. Fibrinogens contribute to platelet aggregation, which can lead to a higher risk of thromboembolism[103]. According to a cross-sectional study performed in T2D patients, plasma fibrinogen level was correlated with increased hemoglobin A1c level, as well as associated with a decreased glycemic status[104].

In addition to fibrinogen, the imbalance of other coagulation factors such as antihemophilic factor (factor VIII), prothrombin (factor II), and thromboplastin (factor III) could cause the impairment of fibrinolysis and prothrombotic imbalance in both MASLD and T2D. This process could induce a hypercoagulable environment[105,106].

Immune cell infiltration

Immune cell infiltration serves a critical role in the progression of metabolic disorders in MASLD and T2D[107-109], as well as in the adipose tissues (Figure 4). Macrophage recruitment and polarization are activated in response to many factors, as elaborated in earlier sections. Elevated M1 macrophage polarization occurs in Kupffer cells, monocyte-derived macrophages, and adipose tissues, which contribute to the proinflammatory response by releasing cytokines, chemokines, and enzymes[110-112]. This process induces and aggravates inflammation. Meanwhile, a decrease in M2 macrophage number further weakens the anti-inflammatory response. In addition to macrophages, B-cell and T-cell infiltration is increased, such as cluster of differentiation (CD) 4^+ T cells and $CD8^+$ T cells[113-115]. Neutrophil activation and monocyte recruitment are also increased[109,116-118].

According to currently published reports related to immune cell infiltration in MASLD and T2D, researchers demonstrate that insulin-related immune cell infiltration increases the risk of fatty liver disease, MASH, and liver fibrosis in T2D patients. The underlying mechanism is attributed to the $CD4^+$ and $CD8^+$ T cell senescence and exhaustion. Furthermore, in diet-induced and chemical-induced mouse MASH models, an increased expression of senescence and exhaustion markers was also detected in liver-infiltrated $CD4^+$ and $CD8^+$ T cells, which emphasizes the roles of T cells in liver disease progression[119-121]. These studies shed light on the importance of immune cell infiltration-oriented therapy on MASLD and T2D management.

NEW MOLECULAR TARGETS IN MACROPHAGES FOR MASLD AND T2D TREATMENT

Tripartite motif containing 38 can regulate M2 macrophage polarization by interacting with heat shock protein family A member 5 to suppress LPS-induced macrophage activation and decrease hepatic steatosis[122]. Treatment of exogenous prostaglandin E2 significantly decreased messenger RNA and protein levels of TNF-α in primary Kupffer cells, peritoneal macrophages, and bone-marrow-derived macrophages induced by LPS. Interestingly, depletion of cyclooxygenase 2 in macrophages can abrogate LPS-induced expression levels of TNF-α proteins in primary Kupffer cells and peritoneal macrophages[123]. Knockout of triggering receptor expressed on myeloid cells 2 ($Trem^2$) in mice with a high-fat diet can exacerbate hepatic steatosis and inflammation, whereas myeloid-specific overexpression of $Trem^2$ can suppress the progression of MASLD[124]. In addition, $Trem^2$ was also found to be upregulated in MASLD or MASH-associated macrophages in human patients, which was associated with liver inflammation and steatosis[124]. Myeloid-specific knockout of gene *Gpnmb* in mice can significantly decrease hepatic steatosis and modestly inhibit liver fibrosis by reducing the formation of lipid-associated macrophages in the liver[33]. Neurogenic locus notch homolog protein-recombination signal binding protein for immunoglobulin kappa J region (Rbpj) signaling pathway regulates monocyte differentiation to macrophages. Rbpj deficiency decreases the differentiation of monocytes to Kupffer cells. In Ly6C-low expressing monocytes, Rbpj deficiency accelerates lipid uptake by upregulating the expression of CD36[125]. Transcriptional factors such as interferon regulatory factor 5 also play important roles in macrophage activation and apoptosis [126].

Similarly, alteration of macrophage function is a key cellular event in T2D. TNF-α-licensed exosome-integrated titanium can promote M2 macrophage polarization by activating autophagy through inhibition of phosphatidylinositol 3-kinase/protein kinase B/mTOR signaling pathway[127]. *Bacteroides Fragilis* and its extracellular vesicles (EVs) can promote vascular calcification in mice with T2D by promoting macrophage M2 polarization[128]. Mechanistically, double-stranded DNAs derived from EVs induce activation of stimulator of interferon response cyclic guanosinc monophosphate-adenosine 5′-monophosphate interactor 1 to promote the phosphorylation of myocyte enhancer factor 2D and increase the expression of tribbles pseudo kinase 1, resulting in macrophage M2 polarization[128].

Moreover, some genes or proteins play important roles in both MASLD and MASH, as well as T2D. For example, the levels of growth differentiation factor-15 (GDF-15) in plasma are increased in patients with obesity with MASLD, T2D, or both due to the accumulation of macrophages in adipose tissues[129]. Suppression of macrophage GDF-15 expression can reduce its plasma level and exacerbate the progression of obesity[129]. Apoptotic vesicles can reprogram macrophages into an anti-inflammatory phenotype in the livers of mice with T2D. Calreticulin functions on the surface of apoptotic

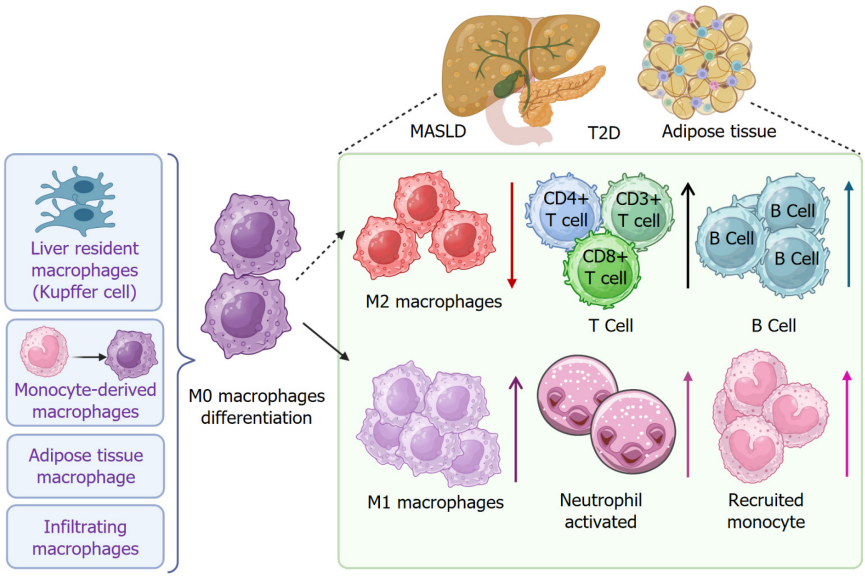

Figure 4 Immune cell infiltration in metabolic dysfunction-associated steatotic liver disease, type 2 diabetes, and adipose tissues. Immune cell infiltration occurs in patients with metabolic dysfunction-associated steatotic liver disease and type 2 diabetes, as well as in adipose tissues. Liver resident macrophages (Kupffer cells and monocyte-derived macrophages), adipose tissue macrophages, and infiltrated macrophages are polarized into M1 macrophages under the pathologic condition. In contrast, M2 macrophage population is decreased. Infiltration of B cells and cluster of differentiation (CD) 3$^+$, CD4$^+$, and CD8$^+$ T cells is increased. Neutrophil activation and monocyte recruitment are increased. T2D: Type 2 diabetes; MASLD: Metabolic dysfunction-associated steatotic liver disease; CD: Cluster of differentiation.

vesicles to regulate macrophage transformation and accumulation[130]. Overall, modulation of macrophage polarization, inflammation, and accumulation during MASLD and T2D can impact disease progression (Table 2).

Table 2 Important signaling pathways regulating macrophage differentiation and function during metabolic dysfunction-associated steatotic liver disease and type 2 diabetes pathogenesis[33,122-130]

Disease	Signaling pathway	Function	Ref.
MASLD	TRIM38-HSPA5 axis	Macrophage M2 polarization	Yang *et al*[122]
MASH	LPS-COX-2-PGE2	Macrophage inflammation	Vahrenbrink *et al*[123]
MASLD	Trem2	Macrophage pyroptosis and inflammation	Xiang *et al*[124]
MASLD	GPNMB	Retention of liver resident Kupffer cells and rerouting monocyte differentiation to Kupffer cell-resembling macrophages	Wang *et al*[33]
MASLD or MASH	Notch-RBPJ	Monocyte-to-macrophage transition	Guo *et al*[125]
MASLD	IRF5	Immunosuppressive and anti-apoptotic function	Alzaid *et al*[126]
T2D	PI3K/AKT/mTOR	Macrophage M2 polarization	Yang *et al*[127]
T2D	STING/Mef2D	Macrophage M2 polarization	Chen *et al*[128]
MASH, T2D	GDF-15	Regulation of obesity	L'homme *et al*[129]
T2D	Calreticulin	Macrophage transformation and accumulation	Zheng *et al*[130]

T2D: Type 2 diabetes; MASLD: Metabolic dysfunction-associated steatotic liver disease; MASH: Metabolic dysfunction-associated steatohepatitis; TRIM38: Tripartite motif containing 38; HSPA5: Heat shock protein family A member 5; LPS: Lipopolysaccharide; COX-2: Cyclooxygenase 2; PGE2: Prostaglandin E2; TREM2: Triggering receptor expressed on myeloid cells 2; GPNMB: Glycoprotein non-metastatic melanoma protein b; Notch: Neurogenic locus notch homolog protein; RBPJ: Recombination signal binding protein for immunoglobulin kappa J region; IRF5: Interferon regulatory factor 5; PI3K: Phosphatidylinositol 3-kinase; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; Mef2D: Myocyte enhancer factor 2D; STING: Stimulator of interferon response cyclic guanosinc monophosphate-adenosine 5′-monophosphate interactor 1; GDF-15: Growth differentiation factor-15.

CLINICAL TRIALS

Clinical trials have evaluated different treatments in patients with T2D and MASLD. For example, a phase 2 clinical trial (No. NCT03459079, https://clinicaltrials.gov/, access date: May 30, 2025) has evaluated the effect of a pan-peroxisome proliferator-activated receptors agonist lanifibranor in regulating intrahepatic triglycerides, hepatic glucose production, DNL, hemoglobin A1c, and lipid profiles, as well as hepatic, adipose tissue, and muscle insulin resistance[131]. One phase 1 clinical study (No. NCT05943886) showed that after 5 weeks of treatment, a dual agonist of glucagon-like peptide-1 and fibroblast growth factor 21 significantly reduced hepatic fat and improved glycemic control, insulin resistance, and lipid profiles in patients with MASLD and T2D[124].

In this section, we review some clinical trials that evaluate the effect of treatments on macrophages in patients with MASLD, T2D, and both or their related metabolic disorders (Table 3).

Table 3 Clinical trials evaluating the roles of macrophages in metabolic dysfunction-associated steatotic liver disease, type 2 diabetes, and other metabolic disorders

Clinical trial	Study type or phase	Disease	Treatment and purpose
NCT04059068	Observational	MASLD	To identify macrophage-derived drug targets to reverse liver disease and reduce macrophage-mediated adipose tissue inflammation
NCT06950710	Observational	MASLD and hepatic ischemia-reperfusion injury	To elucidate the role and mechanisms of macrophage polarization in patients with hepatic ischemia-reperfusion injury and MASLD
NCT06571474	Observational	Obesity, MASLD, T2D	To evaluate the role of transcription factor EB in adipose tissue macrophages in regulating adipose tissue and systemic metabolic function
NCT06007404	Observational	T2D, prediabetes, insulin resistance, obesity	To better understand the role of meta-inflammatory monocytes in adolescent insulin resistance by measuring the influence of body composition, lifestyle habits, and diet
NCT02498119	Observational	T2D	To test the role of arachidonic acid metabolites in the lipid droplets of macrophages
NCT03836443	Interventional	MASLD	To determine the effect of cultured hepatocyte supernatant exposed to MASLD patient plasma on human macrophages *in vitro*
NCT03426111	Interventional	MASH	To evaluate macrophage function in patients treated with endoscopic gastric tubulization and lifestyle modification
NCT05681468	Interventional	T2D, prediabetes, overweight, and obesity	To test the effect of ketogenic diets on immune cell function and inflammation, including macrophages
NCT02768935	Interventional	T2D, cardiovascular complications	To test the infiltration and polarization of macrophages in patients with T2D after myocardial infarction and the role of macrophage miRNAs
NCT02330549	Phase 2	T2D and suspected MASLD	To test the effect of cenicriviroc (152 mg), CCR2 and CCR5 antagonism, on insulin sensitivity in subjects with prediabetes or T2D and suspected MASLD
NCT04521114	Phase 2	MASH	To test the effect of anti-human CCR5 monoclonal antibody leronlimab (PRO 140) on MASH
NCT03151343	Phase 3	T2D, heart disease	To test the effect of SGLT-2 inhibitor on myocardial perfusion, function, and metabolism, as well as adipose tissue macrophage infiltration
NCT02285985	Phase 4	T2D	To test the effect of DPP-4 inhibitor saxagliptin on the reduction of adipose tissue inflammation and macrophage infiltration

NCT: National clinical trials; T2D: Type 2 diabetes; MASLD: Metabolic dysfunction-associated steatotic liver disease; MASH: Metabolic dysfunction-associated steatohepatitis; CCR: C-C chemokine receptor; miRNAs: MicroRNAs; SGLT-2: Sodium glucose co-transport-2; DPP-4: Dipeptidyl peptidase 4.

CONCLUSION

In conclusion, macrophages play an essential role in health and disease. Liver resident macrophages, such as Kupffer cells and monocyte-derived macrophages, as well as adipose tissue macrophages, play a significant role in metabolic-associated diseases such as MASLD and T2D. The crosstalk between the two diseases confers complications on each other due to the various interplays among them, including metabolic pathways, cellular and molecular pathways. Cellular and molecular mechanisms of macrophage-mediated inflammation and immune cell infiltration contribute to the crosstalk between MASLD and T2D. Functionality of macrophage and inflammation in linking MASLD and T2D includes metabolic inflammation, tissue damage, and insulin resistance. Thus, therapeutic targets on macrophage and inflammation in MASLD and T2D possess extensive attraction for future prognostic and therapeutic purposes, especially for individuals with the co-occurrence of MASLD and T2D.

FOOTNOTES

Author contributions: Zhang CY, Liu S, and Yang M designed, wrote, revised, and finalized the manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Country of origin: United States

ORCID number: Chun-Ye Zhang 0000-0003-2567-029X; Ming Yang 0000-0002-4895-5864.

S-Editor: Fan M
L-Editor: A
P-Editor: Xu ZH

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