BMB
Reports

BMB Rep. 2022; 55(4): 166-174
www.bmbreports.org

Invited Mini Review

Roles of heterogenous hepatic macrophages in the progression of liver diseases

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Hepatic macrophages are key immune cells associated with the broad ranges of liver diseases including steatosis, inflammation and fibrosis. Hepatic macrophages interact with other immune cells and orchestrate hepatic immune circumstances. Recently, the heterogenous populations of hepatic macrophages have been discovered termed residential Kupffer cells and monocyte-derived macrophages, and identified their distinct population dynamics during the progression of various liver diseases. Liver injury lead to Kupffer cells activation with induction of inflammatory cytokines and chemokines, which triggers recruitment of inflammatory monocyte-derived macrophages. To understand liver pathology, the functions of different subtypes of liver macrophages should be regarded with different perspectives. In this review, we summarize recent advances in the roles of hepatic macrophages under liver damages and suggest hepatic macrophages as promising therapeutic targets for treating liver diseases. [BMB Reports 2022; 55(4): 166-174]

INTRODUCTION

The liver is the organ that has diverse functions such as numerous protein synthesis, metabolizing drugs and nutrients, and recycling components of red blood cells (1). Disorders of hepatocyte metabolism and other nonparenchymal cells including macrophages cause development of hepatic inflammation and fibrosis which lead to steatohepatitis and cirrhosis (2, 3). Hepatic macrophages are most abundant immune cells in the liver, estimated that 60% of hepatic immune cells are liver macrophages in healthy livers of human and mouse (4). There have been numerous studies that hepatic macrophages could modulate pathophysiological conditions of the liver including hepatotoxicity, inflammation, tissue repair and fibrosis (5). Therefore, understanding the physiological actions of hepatic macrophages for liver diseases is necessary to improve perspectives on therapeutic strategies for curing liver inflammations and fibrotic diseases. Here, we highlight recent findings about roles of heterogenous hepatic macrophages in a pathologic status and open new approach for the treatment of liver diseases.

UNDERSTANDING HETEROGENEITY OF LIVER MACROPHAGES

Hepatic macrophages are most abundant immune cells in the liver. The hepatic macrophages contain different origins derived from yolk sac and bone marrow. The diverse heterogeneity of the liver macrophages are identified based on released cytokines, cell surface markers and transcriptional profiles (5, 6). The subsets of liver macrophages are separated to yolk sac-derived residential Kupffer cells (KCs) and recruited bone marrow (BM)-derived macrophages (monocyte-derived macrophages; MoMFs) (Fig. 1). The heterogenous subpopulations of liver macrophages can be separately determined by distinct expression of surface markers. In mice, KCs are F4/80^{high}, CD11b^{low} and C-type lectin 4F (Clec4F)^{pos}, while MoMFs are F4/80^{low}, CD11b^{high}, lymphocyte antigen 6 complex locus C1 (Ly6C)$^{pos\ or\ neg}$, CD115^{pos}, and Clec4F^{neg} (7-11) (Table 1). Human hepatic macrophages also share similar marker with murine liver macrophage such as T-cell immunoglobulin and mucin domain containing 4 (TIMD4) and macrophage receptor with collagenous structure (MARCO) (Table 2). The circulating monocytes can differentiate toward hepatic MoMFs, which are derived from BM CX3CR1^{pos}CD117^{pos} Lin^{neg} progenitor cells (12). Furthermore, hepatic MoMFs are divided to distinct subsets according to Ly6C expression: inflammatory Ly6C^{pos} MoMFs and restoring Ly6C^{neg} MoMFs (Table 1).

Kupffer cells (KCs)

KCs were named derived from the Karl Wilhelm von Kupffer who initially described these cells as hepatic sinusoidal endothelial cells (13). Later, they were corrected as macrophages by Browic, and then were included in the mononuclear phagocyte system considered as the liver-resident monocyte-derived macrophages (14, 15). But, numerous fate-mapping studies have completely revealed the dogma of the origin of residential macrophages including KCs (16-18).

The development of tissue resident macrophages occurs asyn-

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https://doi.org/10.5483/BMBRep.2022.55.4.022

Received 3 February 2022, Revised 2 March 2022, Accepted 5 March 2022

Keywords: Inflammation, Kupffer cells, Macrophage, Monocytes, NAFLD

ISSN: 1976-670X (electronic edition)

chronously at multiple anatomical locations. The first wave, primitive hematopoiesis, initiates at embryonic day 7.5. which primitive erythroid progenitors from the yolk sac (YS) become primitive erythroblast (19). In the second wave, transient hematopoiesis is the migration of erythro-myeloid progenitors (EMPs) in the yolk sac at embryonic day 8.5 into the bloodstream and localize to the fetal liver. These cells develop to the pre-macrophages until embryonic day 16.5. KCs are mainly yolk sac derived origins populated by second wave and marginally recapitulated by hematopoietic stem cell-derived monocytes after 1 year age mice generating heterogeneity of liver macrophages (20, 21). The definitive hematopoiesis is the third wave that hematopoietic stem cells from the aorta-gonad-mesonephros regions and umbilical/vitelline arteries move to fetal liver and differentiate into resident macrophages (19, 21).

KCs are primarily identified liver macrophage populations as $CD45^{pos}$ $F4/80^{pos}$ $CD11b^{low}$ with distinct expression of liver macrophage protein Clec4F. Based on cellular morphology analysis and single cell gene expression profiling, the researchers found two distinct heterogenous KCs, YS-derived KCs (embryonic-derived KCs; EmKCs) and BM-derived KC (monocyte-derived KCs; MoKCs). YS-derived KCs mainly express Tim4 and MARCO, not expressed in BM-derived KCs. YS-derived KCs contain higher phagocytic and pro-inflammatory functions (22).

Kupffer cells highly express scavenger, complement and pattern recognition receptors (PRRs) (e.g. Toll-like receptors [TLRs]) (Fig. 1) (23). These scavenger roles of KCs functions as a guardian for the host defense against microorganisms (24). TLRs in KCs bind to pathogen-associated molecular patterns (PAMPs) such as bacteria-derived lipopolysaccharide (LPS) to drive an immune response to remove microorganisms (25). CRIg is unique complement receptor to mediate host defense of KCs via binding of the complement factors to activate phagocytose pathogens (26). Furthermore, CRIg has ability to directly capture lipoteichoic acid (LTA) from gram-positive bacteria in the liver sinusoidal circulatory systems acting as PRR, not depending on complement factors (27).

Kupffer cells modulate immune surveillance via antigen uptake and presentation to control T cell immunity as antigen presenting cells (24, 28). On the other hand, KCs suppress T cell activation via release of immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor β (TGFβ) (29).

Monocyte-derived macrophages (MoMFs)

Circulating bone marrow-derived monocytes can infiltrate into the liver when hepatic injuries cause hepatic macrophage niche (6). The recruitment of MoMFs is mainly initiated via increased secretion of chemokine (C-C motif) ligand 2 (CCL2) from KCs or hepatic stellate cells (HSCs) (Fig. 1) (30-32). MoMFs include expression markers such as chemokine CX3-C motif receptor 1 (CX3CR1), Ly6C, CD11b and chemokine (C-C motif) receptor 2 (CCR2), not express Clec4F (11).

Ly6C is important expression marker to distinguish the function of two major populations of MoMFs in the mouse models

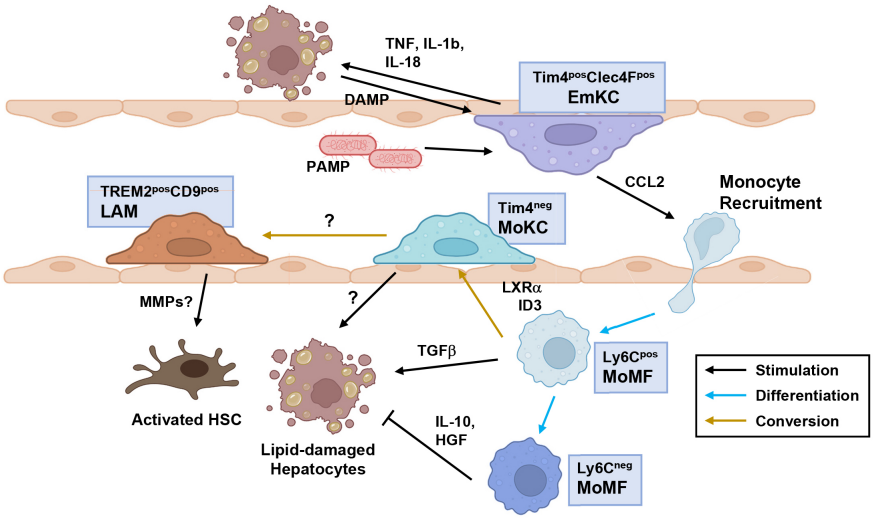

Fig. 1. Roles of heterogenous liver macrophages during the progression of liver injury. Under the pathologic process of liver injury, the resident embryonic-derived Kupffer cells (EmKCs) located inside the sinusoidal endothelium recognize microbial pathogen-associated molecular patterns (PAMPs) and damaged cell-released damage-associated molecular pattern (DAMPs) via PRRs and inflammasome. The activated EmKCs release inflammatory cytokines and CCL2 chemokine to recruit circulating monocytes. They develop into inflammatory $Ly6C^{pos}$ monocyte-derived macrophages (MoMFs) or anti-inflammatory $Ly6C^{neg}$ MoMFs to promote or suppress fibrotic activation of hepatic stellate cells (HSCs). MoMFs can fully differentiate toward monocyte-derived KCs (MoKCs) by activation of LXRα and ID3 transcription factors. TREM2 and CD9 positive lipid-associated macrophages (LAMs) are derived from MoKCs and their roles in the development of liver injury has not been identified yet. The stimulation, differentiation, and conversion of hepatic macrophages are indicated as shown colored arrows.

Table 1. The markers of murine liver macrophage populations

Markers (mouse)	Macrophages					
	EmKCs	MoKCs	LAMs	MoMFs	Monocytes	Neutrophils
CD11b	+	+	+	++	++	++
CD64	+	+	+	++	++	+
F4/80	++	++	++	− To +	−	−
CX3CR1	−	−	−	− To +	+	−
Clec4F	++	+	+	−	−	−
Ly6C	+	−	−	+ To ++	++	++
Ly6G	−	−	−	−	−	++
MHCII	− To +	++	++	+	+	−
Tim4	++	− To +	− To +	−	−	−
TREM2	−	+	++	−	−	−
CD9	−	+	++	−	−	−
Clec2	++	+	−	−	−	−

EmKCs, embyo-derived KCs; MoKCs, monocyte-derived KCs; LAMs, lipid-associated macrophages; MoMFs, monocyte-derived macrophages.

Table 2. The markers of human macrophage populations

Markers (human)	Macrophages			
	KCs	SAMs	MoMFs	Monocytes
MARCO	++	−	−	−
TIMD4	++	−	−	−
MERTK	++	−	−	−
TREM2	−	++	−	−
CD9	−	++	−	−
SPP1	−	++	−	−
CCR2	−	+	++	+
CX3CR1	−	− To +	++	+
APOBEC3A	−	−	++	+
MNDA	−	−	+	++
S100A12	−	−	−	++

SAMs, scar-associated macrophages.

(16, 33). The hepatic Ly6C^{pos} MoMFs mainly recruited by CCL2-CCR2 axis have been suggested as potent proinflammatory and profibrotic cells that induce hepatic inflammation and fibrosis, while Ly6C^{neg} MoMFs which highly express CX3CR1 may have function to restore tissue injuries (30, 34). Ly6C^{pos} MoMFs are precursor monocytes to change toward Ly6C^{neg} MoMFs (16). Unlike YS-derived tissue resident macrophages, MoMFs don't perform self-renewing and have a half-life of 2 days (Ly6C^{neg}) or 20 hours (Ly6C^{pos}) (16). The Ly6C^{pos} MoMFs migrate to the injured sites of the liver and act as inflammatory mediators via expression of PRRs and inflammatory cytokines (35). The Ly6C^{neg} MoMFs exhibit patrolling behavior in the liver and perform restoring tissue injury and scavenging waste of the liver (36, 37). The Ly6C^{pos} MoMFs are mainly derived from bone marrow and recruited to the liver via CCR2, whereas the spleen is the main source for the Ly6C^{neg} MoMFs which infiltrate into the liver through CX3CR1 (38, 39).

In addition to recruitment into injured sites, MoMFs regenerate the liver-resident macrophage pool to fill macrophage niche in the liver. In a mouse model of diphtheria toxin-mediated removal of Clec4F^{pos} KCs, MoMFs reconstituted the hepatic macrophage population and differentiated toward Clec4F^{pos} KCs within 168 hours, suggesting that monocyte can convert toward KCs by hepatic circumstances (7). This process is conducted by the combinational actions of liver sinusoid endothelial cells (LSECs), HSCs and hepatocytes which induce monocyte recruitment and imprinting of the KC signature transcriptional profiles such as inhibitor of differentiation 3 and liver X receptor α (LXRα) (40, 41). Also, MoMFs replace the liver macrophage population after microbial-induced KC death (42), bone marrow transplant into irradiated mice (22), and clodronate-mediated macrophage depletion (36).

HEPATIC MACROPHAGES IN LIVER DISEASES

Dynamic repopulation of macrophages and monocytes subsets in liver diseases

Tissue macrophages serve dual roles for the liver injuries between beneficial versus detrimental functions; friends or foes (43-45). The loss of resident macrophage KCs cause critical consequences in both the injury and recovery phases during scar processing (34, 46). However, general view of MoMFs is that recruitment of pro-inflammatory MoMFs is indispensable to activate regenerative mechanisms as well as overwhelmed inflammation, while unknown mechanisms to increase restorative macrophages recruitment induce inflammation resolution

and tissue repair but also aberrant tissue repair to enhance hepatic fibrosis (11, 47). Indeed, a chronic loss of residential KCs is observed in methionine/choline-deficient (MCD) diet-induced nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC) models (48, 49). The recruitment of MoMFs via CCR2 exacerbates hepatic inflammation in acetaminophen-induced acute liver injury models (35). The pharmacological inhibition of CCR2 attenuates the symptoms of NASH, indicating that early replenishment of MoMFs lead to detrimental consequence to drive liver injuries (30).

It was reported that MoKCs population enhances NASH-induced hepatocyte damages via modulating hepatic triglyceride storage (50). Due to the complex situation of NASH disease, novel hepatic macrophage population-derived from MoKCs has been discovered in human and murine models. These macrophages were identified to scar-associated macrophages (SAM) or lipid-associated macrophages (LAM) since their localization is closely related with fibrotic and lipid droplet area (Fig. 1). SAMs highly express CD9 and triggering receptor expressed on myeloid cells 2 (TREM2), a scavenger receptor for specific glycoproteins and lipids (Table 1, 2) (51, 52). Interestingly, TREM2 expression is positively correlated with nonalcoholic fatty liver disease (NAFLD) histological features such as steatosis, inflammation, and fibrosis (52).

However, functional roles of TREM2^{pos} SAM are not clearly identified to date. These CD9^{pos}TREM2^{pos} SAMs share many similarities in other inflamed tissue-specific macrophages such as adipose tissue in obesity models and brain microglia in Alzheimer's disease (53, 54). Recently, TREM2 deficiency murine models suggest that TREM2 actually has protective roles in various liver injury models (55, 56). However, these models didn't reflect specific depletion of SAMs, only considered the roles of TREM2 protein in the liver injury. Future studies are needed for complete understating of hepatic macrophage heterogeneity during liver injuries and will offer opportunity for novel therapeutic interventions.

Modulation of fibrosis and inflammasome by hepatic macrophages

Liver fibrosis is a general pathological character of most chronic liver diseases (6). Persistent liver injury lead to aberrant wound healing and tissue repair, resulting in excessive accumulation of extracellular matrix (ECM) or failure of ECM degradation. Disturbance of excessive accumulation of hepatic macrophages attenuates liver fibrosis in mice, indicating liver macrophage has profibrogenic roles (32). The several mechanisms of fibrosis progression are involved in macrophage activations. First, KCs increase secretion of CCL2 chemokines to mediate recruitment of pro-inflammatory and fibrotic MoMFs. Second, KCs directly activate HSCs via secretion of fibrotic growth factors such as TGFβ, platelet derived growth factor, and connective tissue growth factor. Third, hepatic macrophages influence HSC activation via proinflammatory cytokines and chemokines such as TNFα, IL-1β, and IL-6.

Because of their central roles in the hepatic microenvironment as recognizer for pathogens, KCs are first-line responders upon liver injury (57). KCs sense pathogens and injured cells via TLRs and damage-associated molecular pattern (DAMP) receptor (Fig. 1) (58). Activation of inflammasome assembly triggers caspase-1-mediated maturation of the inflammatory cytokines IL-1β and IL-18 (59). In the liver, gut-derived pathogens and damaged cell component DAMPs lead to inflammasome activation in KCs (60). KCs increase inflammasome-mediated secretion of IL-1β, which plays a critical role in mediating liver injuries including steatosis and inflammation. In mouse models of chronic liver diseases including MCD and western diet, NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome exacerbate liver inflammation and severity of NASH progression (61). However, inhibition of NLRP3 inflammasome via genetic deletion of NLRP3 and antibody-mediated neutralization of IL-1β didn't show significant difference in acetaminophen-induced acute hepatoxicity model (62).

Interplays with other liver cells

Hepatic macrophages contribute to the pathogenesis of various liver diseases via crosstalk with other liver cell types including LSECs, neutrophils, dendritic cells, natural killer (NK) cells, and platelets. LSECs support the adhesion and migration of circulating monocytes via intercellular adhesion molecule 1 and vascular cell adhesion protein 1, and thereby promote liver regeneration and inflammation in NASH models (63, 64). Increased recruitment of neutrophils is often observed in NAFLD and these cells enhance acute inflammation with disease progression (65). KCs are the major cells to attract neutrophils and interact with these cells to regulate liver inflammation. KCs release CXCL1, CXCL2, and CXCL8 chemokines to recruit neutrophils and other immune cells during various liver injuries (66). The roles of dendritic cells (DCs) in NAFLD pathogenesis are unclear until now, but the recruitment of monocytes by CX3CR1 receptor elevates the number of DCs and affects hepatic inflammation (67). Ly6C^{pos} MoMFs highly express CXCL16 chemokines during liver fibrosis progression by carbon tetrachloride and MCD diet, which promote hepatic recruitment of NKT and T cells to exacerbate liver inflammation (68). KCs can interact with platelet through KC Clec4F and platelet glycoprotein Ib α (69, 70). The blockade of KCs-platelet interaction attenuates liver steatosis, inflammation, and fibrosis during NASH development (70).

SINGLE CELL TRANSCRIPTOMICS TO UNDERSTANDING LIVER MACROPHAGES

In principle, hepatic macrophages could be attractive therapeutic targets to cure liver diseases. However, the findings of the distinct heterogeneity of KCs, MoMFs, and complexity of macrophage niche have caused difficulty to study the therapeutic aspects for liver macrophages. Nevertheless, numerous studies of single cell transcriptomics are solving the key questions to

understand physiology of KCs and MoMFs (51, 71, 72). Single-cell sequencing technology could provide the obvious advantages in an objective manner via unbiased algorithms for macrophage populations. Now, the hepatic macrophage populations were deeply analyzed and finally revealed to be much more heterogenous depending on the disease status (73). This database allows to discover overlooked clusters and potential genes for identity of hepatic macrophages.

Furthermore, single cell transcriptomics can be used to obtain insights for macrophage and other cell interactions. Xiong *et al*. clarified the interplay between endothelial cell, HSC, and hepatic macrophages in the progression of NASH (52). This group conducted single cell sequencing of liver non-parenchymal cells and found NASH-associated macrophages expressing TREM2 and CD9. Through analysis of vascular signaling via single cell sequencing, the author revealed that endothelial cell and liver macrophages were regulated by secretion factors "stellakines" from HSC. Also, other single cell study is focused on non-parenchymal cells obtained from human cirrhotic patients (51). They profiled the transcriptomes of over 100,000 human single cells and also observed the appearance of cirrhotic-associated TREM2 and CD9 positive hepatic macrophages. Interestingly, they conducted interaction studies between endothelial cells, macrophages and HSCs, and described pro-fibrogenic pathways by TREM2 positive macrophages which are similar populations of lipid-associated macrophages to regulate adipocyte hypertrophy and fat accumulation during obesity (51, 53).

However, we should not exclude potential hurdles of single cell transcriptomics studies. The cell numbers might be too low to conclude immune cell populations. The sequencing analysis provides superficial and subtle findings for gene signatures because this technology could not detect enough gene numbers (74). Also, difficult isolation of residential KCs due to weak survival displayed bias of analyzing results for particular immune cell populations. Therefore, massive analysis of single-cell populations and detecting high number of genes is urgently needed to clarify roles of hepatic macrophages in liver diseases.

MACROPHAGE-MEDIATED THERAPEUTIC APPROACHES IN LIVER DISEASES

Multiple approaches to search novel therapies for liver diseases have been endeavored that target diverse key pathway to regulate disease progression (75). Hepatic macrophages have a role as first-line responders for liver injuries which promote or inhibit progression of liver diseases. Therefore, targeting liver macrophages are intriguing therapeutic strategy. Even if most liver macrophage reports were focused on animal-based models, there are some clinical trials already conducted. Approaches with targeting liver macrophages are categorized as inhibition of inflammatory cell recruitment, macrophage activation, and reshaping of macrophage polarization (Table 3).

Blockade of inflammatory monocyte recruitment

As mentioned above, the recruitment of inflammatory MoMFs amplify and exacerbate hepatic inflammation (Fig. 1). The chemoattractant properties of chemokine and receptor interactions; CCL2-CCR2, CCL5-CCR5 and CXCL10-CXCR3, promote infiltration of inflammatory monocytes and reshape of MoMFs (76). Pharmacological drugs to interfere chemokine signaling exist and proved efficacious in diverse experimental animal models for liver diseases including antibodies, small-molecule inhibitor and receptor antagonist (77). In particular, a dual CCR2/CCR5 inhibitor, called cenicriviroc (CVC), was intensively studied and tested for treating NAFLD (78, 79). CVC has been shown to effectively block CCL2-mediated monocyte recruitment and to reduce liver inflammation and fibrosis. Furthermore, CVC was tested in a fully randomized phase IIb clinical trials including 289 patients with NASH and fibrosis, and showed significant improvement of histological stage of liver fibrosis after 1 and 2 years of treatment (80, 81). A phase 3 trials of CVC (NCT03028740) involving approximately 2,000 patients with NASH was conducted, but it was early terminated since lack of efficacy was found based on the early results (82). Other inhibitors of chemoattractant signaling such as maraviroc, a CCL5/RANTES inhibitor, and propagermanium, a CCR2 inhibitor, displayed amelioration of NAFLD/NASH in murine models

Table 3. Potential therapeutic targeting of hepatic macrophages in clinical trials

Strategy	Drug	Mode of action	Clinical trial	Ref
Monocyte recruitment blockade	Cenicriviroc	CCR2/CCR5 inhibitor	Phase 3 termination	(80-82)
	Maraviroc	CCR5 inhibitor	Pre-clinical	(83)
	Propagermanium	CCR2 inhibitor	Pre-clinical	(84)
Inhibitor of Kupffer cell activation	Serelaxin	TLR4 antagonist	Pre-clinical	(90)
	MCC950	NLRP3 inflammasome blocker	Phase 2 termination	(61)
	Selonsertib	ASK1 inhibitor	Phase 3 termination	(92, 93)
Reshaping of macrophage polarization	JC1-40	RORα agonist	Pre-clinical	(94)
	Belapectin	Galectin-3 inhibitor	Phase 2	(98)
	Lanifibranor	Pan-PPAR agonist	Phase 2	(99)

(83, 84).

Dampening of Kupffer cell activation

Kupffer cells initiate inflammatory cascades in the liver by several mechanisms. KCs can be activated through DAMPs/PAMPs-induced NF-κB signaling and inflammasome activation. Also, bacterial translocation via disruption of the gut barrier promotes to TLR4-dependent KC activations (85). Therefore, broad spectrum antibiotics and influencing intestinal permeability could reduce endotoxin-mediated steatohepatitis, fibrosis and hepatocarcinogenesis in mice models (86-88). The TLR4 is a critical receptor for PAMP-induced liver macrophage activation, showing that genetic knockout of TLR4 displayed protective effects on NAFLD and NASH (88, 89). Thus, TLR4 antagonists serelaxin (RLX030) displayed additional effects combined with the PPARγ agonist rosiglitazone to ameliorate liver fibrosis (90). Blockade of NLRP3 inflammasome with treatment of MCC950 effectively reduced liver inflammation and fibrosis in the experimental murine NASH model (61). Hepatocytes and liver macrophages contain similar intracellular pro-inflammatory signaling pathways such as NF-κB, JNK, or ASK1 (91). In particular, ASK1 inhibitor, selonsertib, showed effect on macrophage inactivation, and tested even in human NASH patients. In a phase 2 trial, selonsertib reduced severity of NASH patients, but did not show promising results in phase 3 randomized studies in NASH patients with cirrhosis (92, 93).

Reshaping of macrophage polarization and programming

Due to the dynamic change of macrophage polarization, therapeutic strategies to reshape from the proinflammatory status to regenerative polarization could be a beneficial option for the treatment of hepatic diseases. Nuclear receptor RORα could induce polarity switch of KCs from proinflammatory to antiinflammatory M2 phenotypes to resolve hepatic inflammation in NASH diseases (94). The oral administration of RORα agonists, JC1-40 and Maresin 1, dramatically recovered from high fat diet-induced NAFLD symptoms via activation of M2 liver macrophages (94, 95). The galectin-3, a β-galactoside-binding lectin mainly expressed on macrophages, has been identified to induce inflammatory signaling and HSC activation (96). The galectin-3 inhibitor, belapectin, positively alleviates liver fibrosis in preclinical NASH mouse models (97). However, clinical trials didn't show positive results to reduce hepatic fibrosis in NASH patients (98). PPARs are also strong inducer for M2 macrophage phenotypes. Lanifibranor, a pan-PPAR agonist, decreased steatosis, inflammation, and fibrosis with anti-inflammatory action of murine macrophages (99). Also, the accumulation of pro-inflammatory MoMFs was reduced by treatment of lanifibranor in preclinical choline-deficient, amino acid-defined high-fat diet (CDAA-HFD) and western diet model (99). Now, lanifibranor is under phase 2 clinical trial for NASH patients (NCT03008070). Diverse murine models and cutting-edge technology allow to identify novel molecular mechanisms underlying polarity switch and reprogramming of pro-inflammatory macrophages into restorative functions in the liver, which leads to expand new translational therapeutic approaches.

CONCLUDING REMARKS

In summary, numerous studies in recent years have improved our insights of hepatic macrophages and their homeostatic functions in the liver diseases. These researches give the opportunity to plan novel therapeutic strategy targeting hepatic macrophages. There are some advantages to develop therapeutic targeting of hepatic macrophages: i) Macrophages are crucial drivers for liver inflammation and fibrosis. ii) Major pathways of MoMFs recruitment and macrophage activation are well conserved between human and mouse. iii) Specific targeting to hepatic macrophages can be easily performed due to liver macrophage-specific surface molecules or scavenging functions. However, developing hepatic macrophage-mediated therapy against liver diseases has some challenges: i) Animal models has a limitation to reflect human macrophage functions in diseases stage. ii) The heterogeneity of human hepatic macrophages is less defined compared to mouse models. iii) Technical hardness to isolate human and mouse hepatic macrophages cause bias to interpret results.

In spite of these challenges, the rapid development of knowledge associated with the mechanisms of hepatic macrophages has unraveled the large spectrum of macrophage heterogeneity and immunomodulatory functions in liver diseases. Taken together, the integrated understanding of hepatic macrophages in liver diseases can offer promising points for therapeutic interventions to treat liver diseases in the clinic.

ACKNOWLEDGEMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2021R1C1C1004023 and 2021R1A4A3031661).

CONFLICTS OF INTEREST

The authors have no conflicting interests.

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