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REVIEW

Liver Regeneration in Chronic Liver Injuries: Basic and Clinical Applications Focusing on Macrophages and Natural Killer Cells

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SUMMARY

This review summarizes the role of macrophages and NK cells in liver progenitor-like cell (LPLC)-induced liver regeneration during chronic liver injuries. Macrophages are beneficial to the proliferation and differentiation of LPLCs. NK cells can promote LPLC-induced liver regeneration, but overactivation may lead to high serum levels of IFN-γ, thus inhibiting liver regeneration.

BACKGROUND & AIMS: Liver regeneration is a necessary but complex process involving multiple cell types besides hepatocytes. Mechanisms underlying liver regeneration after partial hepatectomy and acute liver injury have been well-described. However, in patients with chronic and severe liver injury, the remnant liver cannot completely restore the liver mass and function, thereby involving liver progenitor-like cells (LPLCs) and various immune cells.

RESULTS: Macrophages are beneficial to LPLCs proliferation and the differentiation of LPLCs to hepatocytes. Also, cells expressing natural killer (NK) cell markers have been studied in promoting both liver injury and liver regeneration. NK cells can promote LPLC-induced liver regeneration, but the excessive activation of hepatic NK cells may lead to high serum levels of interferon-γ, thus inhibiting liver regeneration.

CONCLUSIONS: This review summarizes the recent research on 2 important innate immune cells, macrophages and NK cells, in LPLC-induced liver regeneration and the mechanisms of liver regeneration during chronic liver injury, as well as the latest macrophage- and NK cell-based therapies for chronic liver injury. These novel findings can further help identify new treatments for chronic liver injury, saving patients from the pain of liver transplantations. *(Cell Mol Gastroenterol Hepatol 2022;■:■–■; https://doi.org/10.1016/j.jcmgh.2022.05.014)*

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The liver is a unique organ because of its strong regeneration ability when it is damaged. After the injury occurs, it can often restore its original size and function in a short period of time.[1] Liver regeneration can be more precisely defined as compensatory hyperplasia in which the remaining liver tissue expands to meet the metabolic demands of the body. In cases of partial hepatectomy (PHx) and acute liver injury (ALI), the damaged area can be replaced by the replication of existing hepatocytes.[2–4] The underlying mechanisms have been finely described.

In contrast, the regeneration in chronic liver diseases is usually involved with liver progenitor-like cells (LPLCs) and various immune cells and often accompanied by extensive necrosis and apoptotic areas,[4,5] thus requiring deep understanding in LPLC-induced regeneration. LPLCs, which are potentially residing in the canals of Hering, are activated in the context of severe chronic liver injury. After activation, LPLCs can proliferate into both hepatocytes and cholangiocytes, thus inducing liver regeneration.[6] Because liver injury that accompanies LPLC responses is often associated with inflammation and fibrosis, scientists have researched the interaction between LPLCs and immune cells. This review aims to summarize and clarify the role of 2 important subsets of innate immune cells, macrophages and natural killer (NK) cells, in LPLC-induced liver regeneration during chronic liver injury, thus providing new insights into potential new treatments for chronic and severe liver diseases.

Liver Regeneration in Chronic Liver Diseases

With a strong ability to regenerate, the liver can restore its original size and function within a short period of time. When part of the liver parenchyma is lost or damaged, such as PHx or ALI, the remaining hepatocytes can quickly enter the cell cycle to supplement and regenerate the liver, which is called compensatory proliferation. Under these circumstances, Wang et al[7] reported that the self-renewing cells adjacent to the central vein of the liver lobule, Wnt-

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Abbreviations used in this paper: **ALI, acute liver injury; BEC, biliary epithelial cell; BMDM, bone marrow-derived macrophage; FGF, fibroblast growth factor; Fn14, fibroblast growth factor-inducible 14; HGF, hepatocyte growth factor; Hh, hedgehog; HSC, hepatic stellate cell; HybHP, hybrid hepatocytes; IFN, interferon; IL, interleukin; MH, mature hepatocyte; natural killer, natural killer; NKT cells, cells expressing NK and T-cell markers; PHx, partial hepatectomy; PTEN, phosphatase and tensin homolog; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TWEAK, tumor necrosis factor-like weak apoptosis inducing factor.**

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responsive Axin2$^+$ hepatocytes, could subserve homeostatic hepatocyte renewal. These specific hepatocytes express stem cell marker Tbx3, which is widely expressed in early liver hepatoblasts and is important for the initiation of hepatocyte differentiation,[8,9] thereby exhibiting unipotent stem cell-like characteristics. However, with a deeper investigation in Axin2$^+$ hepatocytes, Sun et al[10] demonstrated that the liver regeneration induced by PHx was enabled by the proliferation of hepatocytes throughout the liver, rather than by a pericentral population described before. In detail, hepatocytes throughout the liver could upregulate Axin2 after PHx and ALI, thus contributing to the liver regeneration. This controversy may be due to the use of Axin2 heterozygous mice model, which would result in the proliferation of Axin2$^+$ hepatocytes over time. No matter which type of hepatocytes is responsible for the restoration, the liver regeneration after PHx and ALI only induces the proliferation of residual hepatocytes to restore liver mass. However, when chronic injury leads to acute loss of a large number of parenchymal tissues or exhausted hepatocyte proliferation ability, the regeneration process during chronic liver diseases was not mediated by the remaining hepatocytes. According to the severity of the chronic liver injury, 2 types of cells can be alternatively activated. Under severe or chronic injury conditions most hepatocytes become unresponsive. Font-Burgada et al[11] have identified a novel hepatocyte population and name hybrid hepatocytes (HybHP), which constitutively reside in portal triads of healthy liver and express low amounts of Sox9 and normal amounts of HNF4α. They show higher repopulation potential than conventional hepatocytes without originating hepatocellular carcinoma.[11] However, if the injuries persist and the proliferation of HybHP and other hepatocytes fail to restore the liver, LPLCs with positive biliary epithelial cell (BEC) markers will be alternatively activated.[5] The persistent chronic liver injury will severely impair the hepatocyte proliferation ability through excess inflammation, scarring, and epithelial abnormalities.[4] Also, when the damage become extensive and sustained, HybHP will be killed, no longer contributing to the regeneration process.[11] Thus, the alternatively activated LPLCs play an essential role in severe chronic liver injury. LPLCs have bipotent capacity to differentiate into both mature hepatocytes (MHs) and BECs with a capacity for duct formation.[12] In addition, the in vivo injection of dedifferentiated LPLCs in vitro has been proved to repopulate chronically injured liver tissue with high efficiency.[13] According to the studies conducted by Shin et al,[14,15] Forkhead box L1 LPLCs and their descendants are required for the development of hepatocytes after chronic liver injuries, especially contributing to the liver parenchyma during the recovery phase. During the injury phase, LPLCs are responsible for the supply of newly formed hepatocytes, which can remove excessively accumulated fat.[15]

Activation and Expansion of Liver Progenitor-Like Cell–Induced Liver Regeneration

The activation and expansion of LPLCs have been detected in patients with various liver diseases such as alcoholic and nonalcoholic liver disease,[16] chronic viral hepatitis,[17,18] and cholestatic hepatitis.[19] In humans, the combination of hepatocyte loss and impaired hepatocyte proliferation is required to activate the proliferation of LPLCs, because there has been discovered an inverse correlation between the number of LPLCs and the number of hepatocytes expressing Ki67.[20] On the basis of the characteristic markers for LPLCs (CK19, EPCAM, Foxl1, Sox9, NCAM), the possible origins of LPLCs include BECs, hepatoblasts in fetal liver, bone marrow cells, and hepatic stellate cells (HSCs).[21,22]

Hedgehog (Hh) ligands are LPLCs proliferation activators. With the increase in death rate of hepatocytes, dying hepatocytes in chronic liver injuries have been proved to generate Hh ligands. Because Hh ligands are viability factors for LPLCs and myofibroblasts, they can then activate LPLC-induced liver regeneration but also induce fibrogenesis.[23] In addition to its direct effect on LPLCs, Hh ligands also have capacity to indirectly enhance the proliferation of LPLCs by activating HSCs into matrix-producing myofibroblasts.[24] Ruddell et al[25] have suggested that lymphotoxin beta receptor on HSCs may be involved in paracrine signaling with nearby lymphotoxin beta receptor–expressing LPLCs, which is consistent with earlier research that identified the paracrine signaling between HSCs and LPLCs.[26]

Several studies have demonstrated the important role of tumor necrosis factor-like weak apoptosis inducing factor (TWEAK) pathway in the initiation and expansion of LPLCs.[27–30] Because TWEAK has no effect on mature cells, it has a selective mitogenic effect for LPLCs, stimulating the proliferation of LPLCs through its receptor fibroblast growth factor-inducible 14 (Fn14).[27] In a choline-deficient ethionine-supplemented diet mouse model of chronic liver injury, LPLC numbers reduced significantly in Fn14$^{-/-}$ mice. The stimulation of TWEAK led to the activation of nuclear factor kappa B and dose-dependent proliferation of LPLCs, indicating that TWEAK can act directly and stimulate LPLC mitosis in an Fn14-dependent and nuclear factor kappa B–dependent fashion.[28] On the basis of the detected mRNA expression of TWEAK in monocyte and macrophage cell population,[31,32] Kupffer cells or infiltrating macrophages are believed to be the source of endogenous TWEAK. Because of the fact that TWEAK blockade or the Fn14 deficiency does not completely inhibit the proliferation of LPLCs,[27] other pathways appear to be involved in activating their proliferation.

Considering the associated inflammation and fibrosis in LPLC-induced liver regeneration, immune cells and fibroblastic cells surrounding LPLCs are determined important in regulating the process. Cell-to-cell interactions involve paracrine growth factors that can be grouped into several major families,[33] among which the fibroblast growth factor (FGF) family has been identified to be related to the epithelial morphogenesis, repair, and cyto-protection.[34] As a member of FGF family, FGF7 expression has been proved to induce concomitantly with LPLC response in mouse models of liver injuries, identifying FGF7 as a potential therapeutic target for liver diseases. In addition, FGF9 is expressed in hepatocytes, serving as a mediator of hepatocyte

proliferation. Liu et al[35] have demonstrated that LPLCs can be induced to differentiate into hepatocyte-like cells in the presence of FGF9, as well as hepatocyte growth factor (HGF), suggesting the role of FGF family not only in the initiation of LPLC but also in the differentiation of LPLC into hepatocytes.

Differentiation of Liver Progenitor-Like Cell–Induced Liver Regeneration

With the bipotent capacity to differentiate into both MHs and BECs, inducing LPLCs to differentiate into hepatocytes is another important process in LPLC-induced liver regeneration. HGF was originally characterized as a potent mitogen for MHs,[36] with its biological effects mediated by a single tyrosine kinase receptor c-Met.[37] It is not surprising to find that HGF/c-Met signaling acts as an essential pathway for the differentiation of LPLCs and is required for the induced liver regeneration.[38]

The antagonistic interplay between Wnt and Notch signaling has been reported to crucially affect liver regeneration in fibrotic liver.[39,40] The balance of these 2 signalings can determine the direction of LPLC differentiation. Playing a crucial role in the regeneration of chronic liver diseases, the Wnt signaling has been studied in various mouse models.[39,41–47] During hepatocyte regeneration, macrophage derived Wnt3a maintains Numb expression, thereby inhibiting Notch signaling.[41,42] With its direct influence on LPLCs, Wnt3a secreted from macrophages can promote the differentiation toward hepatocytes.

Other pathways involved in the activation and expansion of LPLCs have also been researched, including thyroid hormone signaling,[48,49] HIPPO/YAP pathway,[50–53] and Jag1/Notch signaling.[54–57] The various roles of above-mentioned pathways in LPLC initiation and proliferation are summarized in Figure 1.

Macrophage in Liver Progenitor-Like Cell–Induced Liver Regeneration

Because inflammation has been demonstrated to initiate tissue repair by elimination of the causes of injury such as infectious agents and necrotic cells,[58,59] increasing number of studies have been carried out to identify the roles of immune cells in chronic liver injury-induced liver regeneration (Figure 2). In response to liver injury, liver tissues may initiate the activation of various immune cells, among which the macrophages play a predominant role. In addition to the liver-resident macrophages, also named Kupffer cells, which represent nearly 20% of the liver nonparenchymal cells, hepatic macrophages may also be derived from infiltrating blood monocytes.[60,61] As the immune barrier of liver tissue, Kupffer cells can influence other immune cells through complex cell-cell interactions and secretion of cytokines.[62]

Macrophages influence both the proliferation and differentiation of LPLCs. Kupffer cells or infiltrating macrophages are believed to be the source of endogenous TWEAK.[31,32] A direct link has been proved between macrophage TWEAK production and paracrine signaling associated with DRs, leading to the expansion of LPLCs in TWEAK/Fn14$^{-/-}$ mice model.[30] In addition to the TWEAK signaling, macrophages are also associated with Wnt and Notch signaling, thus playing a crucial role in the differentiation of LPLCs into hepatocytes. Wnt3a has been proved to be expressed by macrophages as a result of the phagocytosis of biological debris, implicating the influence of macrophages on environmental sensing and correction of epithelial repair from LPLCs.[41,63] In detail, the depletion of Kupffer cells did not influence the proliferation of LPLCs but reduced their invasive behavior.[64] The direct cell-cell communication between LPLCs and myofibroblasts has been shown to involve the interactions of lymphotoxin β,[25] as well as the role of extracellular matrix deposition in LPLC expansion and differentiation.[65] The reduction in LPLC parenchymal invasion by the depletion of Kupffer cells has been proved to be attributed to the reduced activation of myofibroblasts and the decrease in the extracellular matrix framework, which is necessary for cell motility.[64]

It has been well-described that the polarization of macrophages plays an important role in liver injury and liver regeneration, with a pro-inflammatory M1 polarization and an alternative anti-inflammatory M2 polarization.[66,67] Similar to the opposite polarization types of macrophages, infiltrating monocytes can also be separated into 2 subtypes characterized by different Ly-6C (Gr-1) expression levels in mice, Ly-6C^{high} monocytes, which are considered to promote tissue injury, and Ly-6C^{low} monocytes, which can suppress inflammation and facilitate liver repair.[68–70] In an ALD mouse model, Ly6C^{high} monocytes were found to develop progressively into Ly6C^{low} monocytes upon phagocytosis of apoptotic hepatocytes in mild liver injury. However, in cases of severe injury, the phenotype switching from Ly6C^{high} to Ly6C^{low} monocytes might be blocked, thereby resulting in persistent hepatic inflammation and impaired liver injury.[61] Also, macrophage polarization has a key role in the progression of nonalcoholic fatty liver disease, driving LPLC response by Wnt3a production.[42] Kupffer cells also turned out to control the initial accumulation of monocyte-derived macrophages, which in turn are responsible for LPLCs proliferation.[71] Furthermore, Viebahn et al[72] identified potential synergy between LPLCs and macrophages through ligand-receptor interaction, which is based on the recruitment of macrophages to the damaged liver by LPLCs.

Natural Killer Cells in Liver Progenitor-Like Cell–Induced Liver Regeneration

Another important innate immune cell subset in liver regeneration is NK cell, which constitutes 30%–50% of the intrahepatic lymphocytes in humans, playing a vital role in suppressing hepatic bacterial and viral infections.[73] Although it has been proved that the activation of NK cells inhibited liver regeneration via the production of interferon (IFN)-γ after PHx,[74] the role of NK cells in chronic liver injury was controversial. The activated NK cells in a CCl_4 mouse model turned out to inhibit the liver regeneration via the production of tumor necrosis factor α,[75] which also played a beneficial role in LPLCs proliferation to replace

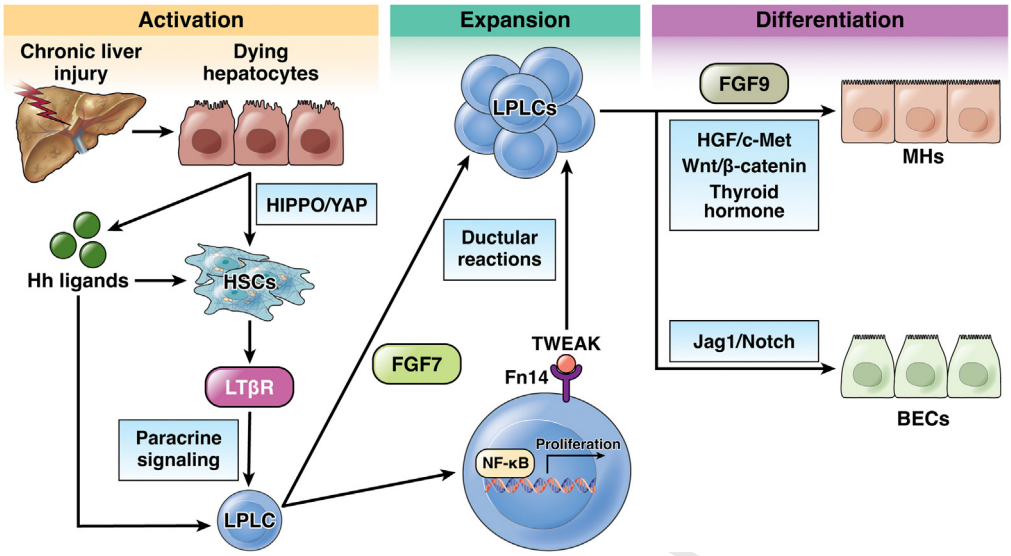

Figure 1. Activation, expansion, and differentiation of LPLCs. During chronic liver injuries, dying hepatocytes generate Hh ligands, which not only directly activate LPLC-induced liver regeneration but also indirectly enhance the proliferation of LPLCs by activating HSCs into matrix-producing myofibroblasts. Also, LTβR on HSCs (activated via HIPPO/YAP pathway) may be involved in paracrine signaling with nearby LTβ-expressing LPLCs. After initiation, TWEAK has a selective mitogenic effect for LPLCs, stimulating the proliferation of LPLCs through its receptor Fn14. The stimulation of TWEAK will lead to the activation of NF-κB and proliferation of LPLCs. FGF not only activates the proliferation of LPLCs (FGF7) but also induces the differentiation of LPLCs into hepatocytes (FGF9). HGF/c-met signaling, Wnt/β-catenin signaling, and thyroid hormone signaling are all proved to promote the differentiation of LPLCs into MHs, whereas Jag1/Notch signaling can induce LPLCs differentiating into BECs. BECs, biliary epithelial cells; FGF, fibroblast growth factor; Fn14, fibroblast growth factor-inducible 14; HGF, hepatic growth factor; Hh ligands, hedgehog ligands; HSCs, hepatic stellate cells; LPLCs, liver progenitor-like cells; LTβR, lymphotoxin β receptor; MHs, mature hepatocytes; NF-κB, nuclear factor kappa B; TWEAK, tumor necrosis factor-like weak apoptosis inducing factor; YAP, Yes-associated protein.

dying hepatocytes.[76] Also, CXCL7 secreted by NK cells could induce the recruitment of mesenchymal stem cells, thereby improving liver regeneration.[77] In addition, conventional NK cells have been proved to predominantly produce interleukin (IL) 22, which could promote the regeneration of epithelial cells and the production of antimicrobial peptides, effectively preventing secondary opportunistic infections during influenza infection.[78] Therefore, NK cells can produce cytokines that are important for liver regeneration.

Considering the negative effect of overactivated NK cells on liver regeneration, researchers have focused on controlling NK cells activation by inhibitory receptors.[79–82] The coinhibitory receptor TIGIT turned out to mediate the self-tolerance of NK cells regenerative hyperplasia by interacting with poliovirus receptor expressed on Kupffer cells, thereby limiting innate immunity against the liver regeneration.[82] Thus, the negative effects induced by the overactivation of NK cells can be potentially reduced by various inhibitory receptors. Considering the possible negative effects of LPLC-induced liver regeneration during chronic liver disease, such as liver fibrosis and hepatocarcinoma, NK cells have also been researched in such diseases. Recently, Saparbay et al[83] have demonstrated that the treatment of Everolimus could enhance the antitumor activity of immature liver-resident NK cells through the up-regulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), consistent with an earlier study showing that liver-resident NK cells were distinctly characterized by expression of TRAIL,[84] which could attack virus-infected and tumor cells.[85] For liver fibrosis, NK cells could kill activated HSCs via RAE1/NKG2D- and TRAIL-dependent mechanisms, thereby controlling and ameliorating liver fibrosis,[86] indicating the important role of NK cells in suppressing liver fibrosis during hepatitis B virus or hepatitis C virus. Furthermore, TWEAK has been proved to play a key role in regulating goat peripheral NK cell cytotoxicity and cytokine expression levels during the progression of PPRV.[87] Because TWEAK signaling contributes to the initiation of LPLCs activation, it may have dual function in LPLC-induced liver regeneration.

Accounting for 10%–15% of human liver lymphocytes, NKT cells, a population of cells expressing NK and T-cell markers,[88,89] have also been studied in liver injury and liver regeneration. Similar to macrophages, NKT cells can also be categorized into pro-inflammatory type I NKT cells and anti-inflammatory type II NKT cells.[90] Type I NKT cells, also called classical or invariant NKT cells, comprise 95% of liver NKT cells and express a semi-invariant T-cell receptor, whereas type II NKT cells comprise less than 5% of liver NKT cells and express more diverse T-cell receptors.[91] Because most of the liver NKT cells have been proved to be invariant NKT, they were initially believed to play a negative role in liver regeneration by releasing cytokines such as IFN-γ and IL4 or direct cytotoxicity. In hepatitis B virus transgenic mice, Dong et al[92] found that the impairment of liver regeneration was not only due to IFN-γ

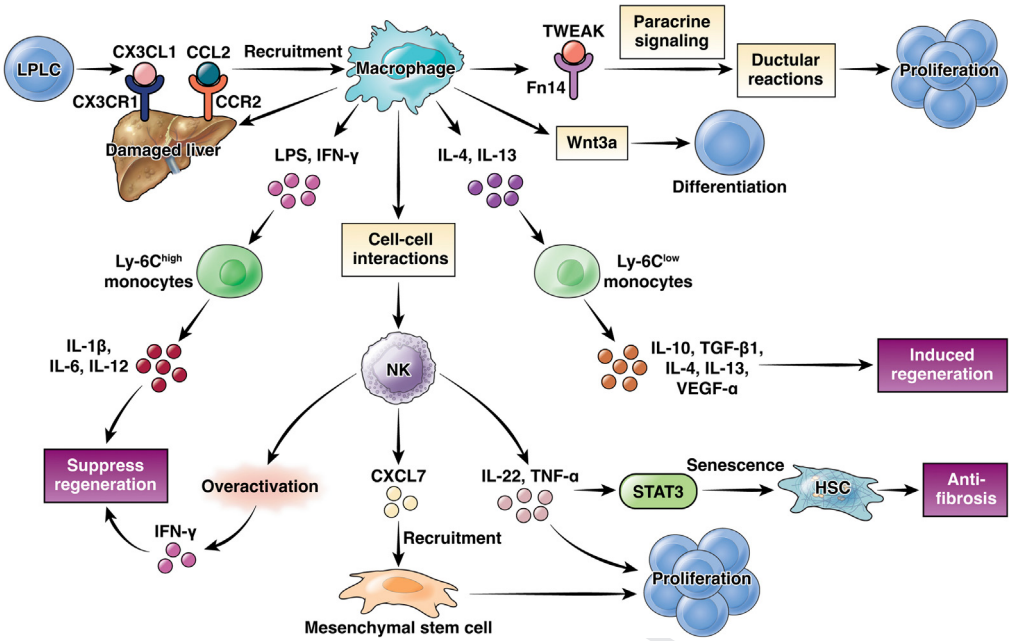

Figure 2. The role of macrophages and NK cells in LPLC-induced regeneration. Macrophages can not only promote the proliferation of LPLCs through TWEAK signaling but also induce the differentiation of LPLCs into hepatocytes via Wnt3a pathway. Ly-6C^{high} monocytes will promote tissue injury by secreting IL-1β, IL-6, and IL-12, whereas Ly-6C^{low} monocytes can suppress inflammation and facilitate liver repair by secreting IL-10, TGFβ1, IL-4, IL-13, and VEGFα. LPLCs can induce the recruitment of infiltrating macrophages to the damaged liver through CCL2/CCR2 and CX3CL1/CX3CR1. Macrophages can also influence other immune cells, including NK cells, through complex cell-cell interactions and secretion of cytokines. NK cells play a beneficial role in LPLCs proliferation, and CXCL7 secreted by NK cells can induce the recruitment of mesenchymal stem cells, thereby improving liver regeneration. Also, IL-22 produced by NK cells and NKT cells can increase HSCs senescence via STAT3 activation, thus alleviating liver fibrosis. CCL2, C-C motif chemokine ligand 2; CCR2, C-C motif chemokine receptor 2; CXCL7, C-X-C motif chemokine ligand 7; CX3CL1, C-X3-C motif chemokine ligand 1; CX3CR1, C-X3-C motif chemokine receptor 1; IFN-γ, interferon γ; IL, interleukin; LPS, lipopolysaccharides; NK cell, natural killer cell; STAT3, signal transducer and activator of transcription 3; TGFβ1, transforming growth factor β-1; TNFα, tumor necrosis factor α; VEGFα, vascular endothelial growth factor α.

overproduction by activated hepatic NKT cells but might also be relevant to hepatocyte itself, which was more sensitive to exogenous stimulus. For direct hepatotoxicity, NKT cells could kill hepatocytes by releasing FasL.[93] However, in chronic liver injury, which will lead to liver fibrosis associated with the accumulation of collagen in the liver,[94] the impact of NKT cells on LPLC-induced liver regeneration seemed to be controversial. Similar to NK cells, NKT cells can inhibit HSC activation by killing activated HSCs, thus inhibiting liver fibrosis. However, the protective effect was only discovered in the earlier stages and not in the later stages of liver fibrosis.[95] Also, IL22 produced by NK and NKT cells has been finely demonstrated to improve liver regeneration by increasing HSCs senescence via STAT3 activation, as well as promoting LPLCs.[96] In addition, the chemokine receptor CXCR6, which is predominantly expressed on NKT cells, could protect liver from inflammation and fibrosis in NEMO^{LPC-KO} mice, in which increased hepatocyte apoptosis and compensatory regeneration caused steatosis, inflammation, and fibrosis.[97] In NKT cell-deficient mice, the impairment of Cyclin B1 and p21 expression could induce reduced liver regeneration.[98] Thus, NKT cells are necessary and even beneficial for LPLCs-induced liver regeneration during chronic liver injury.

Therapies Improve Liver Regeneration Based on Innate Immune Cells for Chronic Liver Disease

With a diversity of complications and the result of liver fibrosis and hepatocarcinoma, the treatment to chronic liver diseases associated with LPLC-induced liver regeneration is an urgent but challenging problem. So far, most of the studies have been carried out on cell therapies based on macrophages. For example, bone marrow cell therapy has shown promising protective results in liver regeneration.[30,99–103] A single infusion of unfractionated bone marrow cells has been proved to result in a direct activation of DRs, as well as the changes in liver structure and function, including LPLCs expansion.[30] More specifically, bone marrow-derived macrophage (BMDM) delivery could lead to early chemokine up-regulation, with hepatic recruitment of endogenous macrophages and neutrophils, thereby attenuating liver fibrosis in chronic liver disease.[99] In addition, the expression of TWEAK, mitogen that is selective for LPCs but not mature hepatocytes,[27] was increased in bone marrow macrophage–treated mice,[99] further improving LPLCs proliferation. Considering the opposite roles of the 2 subsets of macrophages in liver inflammation

and regeneration, another macrophage-based treatment for chronic liver injury can be rendering macrophages toward a more restorative phenotype or directly using polarized macrophages for cytotherapy.[103,104] Baeck et al[104] examined the role of CCL2 inhibitors, which could pharmacologically inhibit Ly6C^{low} macrophage infiltration, with the liver fibrosis regression appeared in both models, indicating that suppressing Ly6C^{low} macrophage infiltration could be a selective strategy for liver regeneration during chronic liver injury.

It has been proved that the M1 polarized BMDMs exhibited better therapeutic effects than non-polarized M0 BMDMs, which was attributed to their ability to attenuate liver fibrosis and improve liver regeneration by recruiting monocyte-derived macrophages and NK cells, thus promoting collagen degradation, HSC apoptosis, and LPLC proliferation.[103] Also, M1 macrophages could further polarize the recruited endogenous macrophages into a Ly6C^{low} restorative phenotype,[103] leading to an improved regeneration in chronic liver diseases. Recently, a new treatment targeting S1PR2, which has emerged to be pro-inflammatory and pro-fibrotic by affecting the infiltration and M1 polarization of bone marrow macrophages,[105–108] was designed and carried out, showing that the inhibition of macrophage S1PR2 could retard liver inflammation and fibrogenesis via down-regulating NLRP3 inflammasome.[109] Therefore, the different polarization phenotypes of macrophages played a crucial role in liver regeneration and provided various methods for the treatment of chronic liver diseases.

Macrophages and NK cells are 2 subsets indispensable for liver regeneration. Therefore, scientists have researched the interplay between them in the hope of better outcomes for chronic liver diseases. Ma et al[110] demonstrated that the deletion of phosphatase and tensin homolog (PTEN), originally identified as a tumor-suppressor protein, could activate the M2 polarization of Kupffer cells, leading to the less activated phenotype of NK cells, probably through direct cell-cell contact or decreased secretion levels of IL12 and IL15. Furthermore, PTEN-deficient Kupffer cells secreted more growth factors required for liver regeneration,[110] identifying PTEN as a potential target for liver regeneration. For NK cells, they have been previously proved to be beneficial for attenuating inflammation and preventing adverse cardiac remodeling via the cell crosstalk with allogeneic human cardiac-derived progenitor cells,[111] implying their potential roles in LPLC-induced liver regeneration. In a Fah$^{-/-}$ liver failure mouse model, the activated NK cells showed a vital role in bone marrow-derived hepatocyte generation, facilitating the fusion of myelomonocyte and hepatocyte in an IFN-γ–dependent manner.[112] With a low efficiency of bone marrow-derived hepatocyte generation, bone marrow transplantation has been used in severe and chronic liver diseases but showed limited efficacy. Clarifying the beneficial role of innate immune cells such as NK cells could greatly improve the outcomes of bone marrow transplantation and bring exciting news to patients with severe liver failure.

In addition, NK cells also showed direct roles in preventing liver fibrosis in a thioacetamide-induced liver fibrosis mouse model through its activation by Fasudil, a Ras homology family member A kinase inhibitor.[113] The activated NK cells could induce HSC apoptosis and clear senescent-activated HSCs, thereby killing HSCs and producing IFN-γ to prevent liver fibrosis,[113] identifying the critical role of IFN-γ in NK cell–related therapy for liver regeneration during chronic liver injury. Interestingly, NK cells could regulate the M1 and M2 polarization of macrophages according to the immune response phase and disease stage during liver injury-induced inflammation.[114] Therefore, synergies between macrophages and NK cells could be further investigated to emphasize the role of innate immune cells in LPLC-induced liver regeneration.

The studies on NKT-based treatment for chronic liver injury were limited to date because of its less importance compared with macrophages and NK cells in liver regeneration. Because NKT cells were considered pathogenic in liver diseases,[115–118] the selective elimination of hepatic NKT cells by concanavalin A showed accelerated liver regeneration after PHx.[115] Correspondingly, the accumulation of NKT cells depending on chemokine receptor CXCR6 resulted in exacerbated inflammation and promoted liver fibrosis.[116] Therefore, targeting CXCR6 might have the potential to treat liver fibrosis. Also, a study on commensal bacteria in liver regeneration demonstrated that this bacteria subset could promote liver regeneration by maintaining Kupffer cell tolerance and preventing the overactivation of NKT cells,[119] which could explain why the overuse of antibiotics induced impaired liver function and liver regeneration. With the in-depth understanding of NKT cells, Martin-Murphy et al[120] proved that NKT cells could protect mice from acetaminophen-induced liver injury probably by producing IL4. It remains unknown whether NKT cells can be developed to promote liver regeneration by taking advantage of 2 subpopulations with opposite effects like macrophages. Thus, further exploration is needed to investigate the therapeutic roles of NK cells and NKT cells in liver regeneration during chronic liver injury.

Conclusions

In summary, macrophages can not only promote the proliferation of LPLCs through TWEAK signaling but also induce the differentiation of LPLCs into hepatocytes via Wnt3a pathway. The macrophage-based cytotherapy has been proved to be beneficial for liver regeneration. In addition, treatments polarizing macrophages to a more restorative phenotype can also help repair the liver. For NK cells, they play a beneficial role in viral hepatitis because of their ability to suppress liver fibrosis, which is the major negative effect of LPLC-induced liver regeneration. However, the overaction of NK cells may lead to the overproduction of IFN-γ, thus leading to impaired liver regeneration. Thus, treatments based on NK cells mainly focus on the control of NK cells activation to take advantage of their beneficial roles. NKT cells, another subset of innate immune cells, can also be categorized into pro-inflammatory

type I and restorative type II NKT cells, but they have been less researched in liver regeneration compared with macrophages and NK cells. Considering the important role of LPLCs in liver regeneration during chronic liver injury, further studies based on these 3 kinds of innate immune cells are required because of their close relationship with LPLCs.

References

1. Mao SA, Glorioso JM, Nyberg SL. Liver regeneration. Transl Res 2014;163:352–362.
2. Bhushan B, Apte U. Liver regeneration after acetaminophen hepatotoxicity. Am J Pathol 2019;189:719–729.
3. Fausto N, Campbell JS, Riehle KJ. Liver regeneration. Hepatology 2006;43:S45–S53.
4. Forbes SJ, Newsome PN. Liver regeneration: mechanisms and models to clinical application. Nat Rev Gastroenterol Hepatol 2016;13:473–485.
5. Itoh T. Stem/progenitor cells in liver regeneration. Hepatology 2016;64:663–668.
6. Ko S, Russell JO, Molina LM, Monga SP. Liver progenitors and adult cell plasticity in hepatic injury and repair: knowns and unknowns. Annu Rev Pathol Mech Dis 2020;15:23–50.
7. Wang B, Zhao L, Fish M, Logan CY, Nusse R. Self-renewing diploid Axin2+ cells fuel homeostatic renewal of the liver. Nature 2015;524:180–185.
8. Suzuki A, Sekiya S, Büscher D, Izpisúa Belmonte JC, Taniguchi H. Tbx3 controls the fate of hepatic progenitor cells in liver development by suppressing p19ARF expression. Development 2008;135:1589–1595.
9. Lüdtke THW, Christoffels VM, Petry M, Kispert A. Tbx3 promotes liver bud expansion during mouse development by suppression of cholangiocyte differentiation. Hepatology 2009;49:969–978.
10. Sun T, Pikiolek M, Orsini V, Bergling S, Holwerda S, Morelli L, Hoppe PS, Planas-Paz L, Yang Y, Ruffner H, Bouwmeester T, Lohmann F, Terracciano LM, Roma G, Cong F, Tchorz JS. AXIN2+ pericentral hepatocytes have limited contributions to liver homeostasis and regeneration. Cell Stem Cell 2020;26:97–107.e6.
11. Font-Burgada J, Shalapour S, Ramaswamy S, Hsueh B, Rossell D, Umemura A, Taniguchi K, Nakagawa H, Valasek MA, Ye L, Kopp JL, Sander M, Carter H, Deisseroth K, Verma IM, Karin M. Hybrid periportal hepatocytes regenerate the injured liver without giving rise to cancer. Cell 2015;162:766–779.
12. Lu WY, Bird TG, Boulter L, Tsuchiya A, Cole AM, Hay T, Guest RV, Wojtacha D, Man TY, Mackinnon A, Ridgway RA, Kendall T, Williams MJ, Jamieson T, Raven A, Hay DC, Iredale JP, Clarke AR, Sansom OJ, Forbes SJ. Hepatic progenitor cells of biliary origin with liver repopulation capacity. Nat Cell Biol 2015;17:971–983.
13. Katsuda T, Kawamata M, Hagiwara K, Takahashi R, Yamamoto Y, Camargo FD, Ochiya T. Conversion of terminally committed hepatocytes to culturable bipotent progenitor cells with regenerative capacity. Cell Stem Cell 2017;20:41–55.
14. Shin S, Upadhyay N, Greenbaum LE, Kaestner KH. Ablation of Foxl1-Cre–labeled hepatic progenitor cells and their descendants impairs recovery of mice from liver injury. Gastroenterology 2015;148:192–202.e3.
15. Shin S, Walton G, Aoki R, Brondell K, Schug J, Fox A, Smirnova O, Dorrell C, Erker L, Chu AS, Wells RG, Grompe M, Greenbaum LE, Kaestner KH. Foxl1-Cre-marked adult hepatic progenitors have clonogenic and bilineage differentiation potential. Genes Dev 2011;25:1185–1192.
16. Roskams T, Yang SQ, Koteish A, Durnez A, DeVos R, Huang X, Achten R, Verslype C, Diehl AM. Oxidative stress and oval cell accumulation in mice and humans with alcoholic and nonalcoholic fatty liver disease. Am J Pathol 2003;163:1301–1311.
17. Lowes KN, Croager EJ, Abraham LJ, Olynyk JK, Yeoh GCT. Upregulation of lymphotoxin β expression in liver progenitor (oval) cells in chronic hepatitis C. Gut 2003;52:1327–1332.
18. Lowes KN, Brennan BA, Yeoh GC, Olynyk JK. Oval cell numbers in human chronic liver diseases are directly related to disease severity. Am J Pathol 1999;154:537–541.
19. Roskams T, De Vos R, Van Eyken P, Myazaki H, Van Damme B, Desmet V. Hepatic OV-6 expression in human liver disease and rat experiments: evidence for hepatic progenitor cells in man. J Hepatol 1998;29:455–463.
20. Katoonizadeh A, Nevens F, Verslype C, Pirenne J, Roskams T. Liver regeneration in acute severe liver impairment: a clinicopathological correlation study. Liver Int 2006;26:1225–1233.
21. Shin S, Kaestner KH. The origin, biology, and therapeutic potential of facultative adult hepatic progenitor cells. In: Current topics in developmental biology, 107. New York: Elsevier, 2014:269–292.
22. Dorrell C, Erker L, Schug J, Kopp JL, Canaday PS, Fox AJ, Smirnova O, Duncan AW, Finegold MJ, Sander M, Kaestner KH, Grompe M. Prospective isolation of a bipotential clonogenic liver progenitor cell in adult mice. Genes Dev 2011;25:1193–1203.
23. Jung Y, Witek RP, Syn WK, Choi SS, Omenetti A, Premont R, Guy CD, Diehl AM. Signals from dying hepatocytes trigger growth of liver progenitors. Gut 2010;59:655–665.
24. Choi SS, Omenetti A, Witek RP, Moylan CA, Syn WK, Jung Y, Yang L, Sudan DL, Sicklick JK, Michelotti GA, Rojkind M, Diehl AM. Hedgehog pathway activation and epithelial-to-mesenchymal transitions during myofibroblastic transformation of rat hepatic cells in culture and cirrhosis. Am J Physiol Gastrointest Liver Physiol 2009;297:G1093–G1106.
25. Ruddell RG, Knight B, Tirnitz-Parker JEE, Akhurst B, Summerville L, Subramaniam VN, Olynyk JK, Ramm GA. Lymphotoxin-β receptor signaling regulates hepatic stellate cell function and wound healing in a murine model of chronic liver injury. Hepatology 2009;49:227–239.
26. Paku S, Schnur J, Nagy P, Thorgeirsson SS. Origin and structural evolution of the early proliferating oval cells in rat liver. Am J Pathol 2001;158:1313–1323.

27. Jakubowski A, Ambrose C, Parr M, Lincecum JM, Wang MZ, Zheng TS, Browning B, Michaelson JS, Baestcher M, Wang B, Bissell DM, Burkly LC. TWEAK induces liver progenitor cell proliferation. J Clin Invest 2005;115:2330–2340.
28. Tirnitz-Parker JEE, Viebahn CS, Jakubowski AS, Klopcic BR, Olynyk JK, Yeoh GCT, Knight B. Tumor necrosis factor-like weak inducer of apoptosis is a mitogen for liver progenitor cells. Hepatology 2010; 52:291–302.
29. Dwyer BJ, Olynyk JK, Ramm GA, Tirnitz-Parker JEE. TWEAK and LTβ signaling during chronic liver disease. Front Immunol 2014;5.
30. Bird TG, Lu WY, Boulter L, Gordon-Keylock S, Ridgway RA, Williams MJ, Taube J, Thomas JA, Wojtacha D, Gambardella A, Sansom OJ, Iredale JP, Forbes SJ. Bone marrow injection stimulates hepatic ductular reactions in the absence of injury via macrophage-mediated TWEAK signaling. Proc Natl Acad Sci 2013;110:6542–6547.
31. Wiley SR, Winkles JA. TWEAK, a member of the TNF superfamily, is a multifunctional cytokine that binds the TweakR/Fn14 receptor. Cytokine Growth Factor Rev 2003;14:241–249.
32. Campbell S. The role of TWEAK/Fn14 in the pathogenesis of inflammation and systemic autoimmunity. Front Biosci 2004;9:2273.
33. Gerhart J. 1998 warkany lecture: signaling pathways in development. Teratology 1999;60:226–239.
34. Steiling H, Werner S. Fibroblast growth factors: key players in epithelial morphogenesis, repair and cytoprotection. Curr Opin Biotechnol 2003;14:533–537.
35. Liu W, Wang Y, Sun Y, Wu Y, Ma Q, Shi Y, He R, Zhang T, Ma Y, Zuo W, Wu Z. Clonal expansion of hepatic progenitor cells and differentiation into hepatocyte-like cells. Dev Growth Differ 2019;61:203–211.
36. Nakamura T, Mizuno S. The discovery of hepatocyte growth factor (HGF) and its significance for cell biology, life sciences and clinical medicine. Proc Jpn Acad Ser B 2010;86:588–610.
37. Trusolino L, Bertotti A, Comoglio PM. MET signalling: principles and functions in development, organ regeneration and cancer. Nat Rev Mol Cell Biol 2010; 11:834–848.
38. Ishikawa T, Factor VM, JU Marquardt, Raggi C, Seo D, Kitade M, Conner EA, Thorgeirsson SS. Hepatocyte growth factor/c-met signaling is required for stem-cell-mediated liver regeneration in mice. Hepatology 2012; 55:1215–1226.
39. Huang M, Chang A, Choi M, Zhou D, Anania FA, Shin CH. Antagonistic interaction between Wnt and Notch activity modulates the regenerative capacity of a zebrafish fibrotic liver model. Hepatology 2014; 60:1753–1766.
40. Mao Y, Tang S, Yang L, Li K. Inhibition of the Notch signaling pathway reduces the differentiation of hepatic progenitor cells into cholangiocytes in biliary atresia. Cell Physiol Biochem 2018;49:1115–1123.
41. Boulter L, Govaere O, Bird TG, Radulescu S, Ramachandran P, Pellicoro A, Ridgway RA, Seo SS, Spee B, Van Rooijen N, Sansom OJ, Iredale JP, Lowell S, Roskams T, Forbes SJ. Macrophage-derived Wnt opposes Notch signaling to specify hepatic progenitor cell fate in chronic liver disease. Nat Med 2012; 18:572–579.
42. Carpino G, Nobili V, Renzi A, De Stefanis C, Stronati L, Franchitto A, Alisi A, Onori P, De Vito R, Alpini G, Gaudio E. Macrophage activation in pediatric nonalcoholic fatty liver disease (NAFLD) correlates with hepatic progenitor cell response via Wnt3a Pathway. In: Syn WK, ed. PLOS One 2016;11:e0157246.
43. Coulouarn C, Cavard C, Rubbia-Brandt L, Audebourg A, Dumont F, Jacques S, Just PA, Clément B, Gilgenkrantz H, Perret C, Terris B. Combined hepatocellular-cholangiocarcinomas exhibit progenitor features and activation of Wnt and TGFβ signaling pathways. Carcinogenesis 2012;33:1791–1796.
44. Boulter L, Guest RV, Kendall TJ, Wilson DH, Wojtacha D, Robson AJ, Ridgway RA, Samuel K, Van Rooijen N, Barry ST, Wigmore SJ, Sansom OJ, Forbes SJ. WNT signaling drives cholangiocarcinoma growth and can be pharmacologically inhibited. J Clin Invest 2015; 125:1269–1285.
45. Russell JO, Monga SP. Wnt/β-catenin signaling in liver development, homeostasis, and pathobiology. Annu Rev Pathol Mech Dis 2018;13:351–378.
46. Preziosi M, Okabe H, Poddar M, Singh S, Monga SP. Endothelial Wnts regulate β-catenin signaling in murine liver zonation and regeneration: a sequel to the Wnt–Wnt situation. Hepatol Commun 2018;2:845–860.
47. Ma Z, Li F, Chen L, Gu T, Zhang Q, Qu Y, Xu M, Cai X, Lu L. Autophagy promotes hepatic differentiation of hepatic progenitor cells by regulating the Wnt/β-catenin signaling pathway. J Mol Histol 2019;50:75–90.
48. Bockhorn M, Frilling A, Benkö T, Best J, Sheu SY, Trippler M, Schlaak JF, Broelsch CE. Tri-iodothyronine as a stimulator of liver regeneration after partial and subtotal hepatectomy. Eur Surg Res 2007;39: 58–63.
49. László V, Dezső K, Baghy K, Papp V, Kovalszky I, Sáfrány G, Thorgeirsson SS, Nagy P, Paku S. Triiodothyronine accelerates differentiation of rat liver progenitor cells into hepatocytes. Histochem Cell Biol 2008; 130:1005–1014.
50. Konishi T, Schuster RM, Lentsch AB. Proliferation of hepatic stellate cells, mediated by YAP and TAZ, contributes to liver repair and regeneration after liver ischemia-reperfusion injury. Am J Physiol Gastrointest Liver Physiol 2018;314:G471–G482.
51. Lu L, Finegold MJ, Johnson RL. Hippo pathway coactivators Yap and Taz are required to coordinate mammalian liver regeneration. Exp Mol Med 2018;50, e423–e423.
52. Moya IM, Halder G. Hippo–YAP/TAZ signalling in organ regeneration and regenerative medicine. Nat Rev Mol Cell Biol 2019;20:211–226.
53. Planas-Paz L, Sun T, Pikiolek M, Cochran NR, Bergling S, Orsini V, Yang Z, Sigoillot F, Jetzer J, Syed M, Neri M, Schuierer S, Morelli L, Hoppe PS, Schwarzer W, Cobos CM, Alford JL, Zhang L, Cuttat R,

Waldt A, Carballido-Perrig N, Nigsch F, Kinzel B, Nicholson TB, Yang Y, Mao X, Terracciano LM, Russ C, Reece-Hoyes JS, Gubser Keller C, Sailer AW, Bouwmeester T, Greenbaum LE, Lugus JJ, Cong F, McAllister G, Hoffman GR, Roma G, Tchorz JS. YAP, but not RSPO-LGR4/5, signaling in biliary epithelial cells promotes a ductular reaction in response to liver injury. Cell Stem Cell 2019;25:39–53.e10.

54. Ortica S, Tarantino N, Aulner N, Israël A, Gupta-Rossi N. The 4 Notch receptors play distinct and antagonistic roles in the proliferation and hepatocytic differentiation of liver progenitors. FASEB J 2014;28:603–614.
55. Lu J, Zhou Y, Hu T, Zhang H, Shen M, Cheng P, Dai W, Wang F, Chen K, Zhang Y, Wang C, Li J, Zheng Y, Yang J, Zhu R, Wang J, Lu W, Zhang H, Wang J, Xia Y, De Assuncao TM, Jalan-Sakrikar N, Huebert RC, Zhou Bin, Guo C. Notch signaling coordinates progenitor cell-mediated biliary regeneration following partial hepatectomy. Sci Rep 2016;6:22754.
56. Zhang F, Zhang J, Li X, Li B, Tao K, Yue S. Notch signaling pathway regulates cell cycle in proliferating hepatocytes involved in liver regeneration: the Notch signaling pathway. J Gastroenterol Hepatol 2018; 33:1538–1547.
57. Yang X, He C, Zhu L, Zhao W, Li S, Xia C, Xu C. Comparative analysis of regulatory role of Notch signaling pathway in 8 types liver cell during liver regeneration. Biochem Genet 2019;57:1–19.
58. Campos G, Schmidt-Heck W, Ghallab A, Rochlitz K, Pütter L, Medinas DB, Hetz C, Widera A, Cadenas C, Begher-Tibbe B, Reif R, Günther G, Sachinidis A, Hengstler JG, Godoy P. The transcription factor CHOP, a central component of the transcriptional regulatory network induced upon CCl4 intoxication in mouse liver, is not a critical mediator of hepatotoxicity. Arch Toxicol 2014;88:1267–1280.
59. Karin M, Clevers H. Reparative inflammation takes charge of tissue regeneration. Nature 2016; 529:307–315.
60. Epelman S, Lavine KJ, Randolph GJ. Origin and functions of tissue macrophages. Immunity 2014;41:21–35.
61. Wang M, You Q, Lor K, Chen F, Gao B, Ju C. Chronic alcohol ingestion modulates hepatic macrophage populations and functions in mice. J Leukoc Biol 2014; 96:657–665.
62. Fernández V, Reyes S, Bravo S, Sepúlveda R, Romanque P, Santander G, Castillo I, Varela P, Tapia G, Videla LA. Involvement of Kupffer cell-dependent signaling in T3-induced hepatocyte proliferation in vivo. Biol Chem 2007;388.
63. Reddy SM, Hsiao KHK, Abernethy VE, Fan H, Longacre A, Lieberthal W, Rauch J, Koh JS, Levine JS. Phagocytosis of apoptotic cells by macrophages induces novel signaling events leading to cytokine-independent survival and inhibition of proliferation: activation of Akt and inhibition of extracellular signal-regulated kinases 1 and 2. J Immunol 2002; 169:702–713.
64. Van Hul N, Lanthier N, Español Suñer R, Abarca Quinones J, van Rooijen N, Leclercq I. Kupffer cells influence parenchymal invasion and phenotypic orientation, but not the proliferation, of liver progenitor cells in a murine model of liver injury. Am J Pathol 2011; 179:1839–1850.
65. Pintilie DG, Shupe TD, Oh S, Salganik SV, Darwiche H, Petersen BE. Hepatic stellate cells' involvement in progenitor-mediated liver regeneration. Lab Invest 2010; 90:1199–1208.
66. Sica A, Invernizzi P, Mantovani A. Macrophage plasticity and polarization in liver homeostasis and pathology. Hepatology 2014;59:2034–2042.
67. Besnard A, Julien B, Gonzales E, Tordjmann T. Innate immunity, purinergic system, and liver regeneration: a trip in complexity. Hepatology 2013;57:1688–1690.
68. Tacke F, Zimmermann HW. Macrophage heterogeneity in liver injury and fibrosis. J Hepatol 2014;60:1090–1096.
69. Vannella KM, Wynn TA. Mechanisms of organ injury and repair by macrophages. Annu Rev Physiol 2017; 79:593–617.
70. Tacke F, Randolph GJ. Migratory fate and differentiation of blood monocyte subsets. Immunobiology 2006; 211:609–618.
71. Elsegood CL, Chan CW, Degli-Esposti MA, Wikstrom ME, Domenichini A, Lazarus K, van Rooijen N, Ganss R, Olynyk JK, Yeoh GCT. Kupffer cell-monocyte communication is essential for initiating murine liver progenitor cell-mediated liver regeneration: liver injury/regeneration. Hepatology 2015;62:1272–1284.
72. Viebahn CS, Benseler V, Holz LE, Elsegood CL, Vo M, Bertolino P, Ganss R, Yeoh GCT. Invading macrophages play a major role in the liver progenitor cell response to chronic liver injury. J Hepatol 2010; 53:500–507.
73. Sun H, Sun C, Tian Z, Xiao W. NK cells in immunotolerant organs. Cell Mol Immunol 2013;10:202–212.
74. Sun R, Gao B. Negative regulation of liver regeneration by innate immunity (natural killer cells/interferon-γ). Gastroenterology 2004;127:1525–1539.
75. Wei H, Wei H, Wang H, Tian Z, Sun R. Activation of natural killer cells inhibits liver regeneration in toxin-induced liver injury model in mice via a tumor necrosis factor-α-dependent mechanism. Am J Physiol Gastrointest Liver Physiol 2010;299:G275–G282.
76. Cosgrove BD, Cheng C, Pritchard JR, Stolz DB, Lauffenburger DA, Griffith LG. An inducible autocrine cascade regulates rat hepatocyte proliferation and apoptosis responses to tumor necrosis factor-α. Hepatology 2008;48:276–288.
77. Almeida CR, Caires HR, Vasconcelos DP, Barbosa MA. NAP-2 secreted by human NK cells can stimulate mesenchymal stem/stromal cell recruitment. Stem Cell Rep 2016;6:466–473.
78. Kumar P, Thakar MS, Ouyang W, Malarkannan S. IL-22 from conventional NK cells is epithelial regenerative and inflammation protective during influenza infection. Mucosal Immunol 2013;6:69–82.
79. Long EO, Sik Kim H, Liu D, Peterson ME, Rajagopalan S. Controlling natural killer cell responses: integration of signals for activation and inhibition. Annu Rev Immunol 2013;31:227–258.

80. Ndhlovu LC, Lopez-Vergès S, Barbour JD, Jones RB, Jha AR, Long BR, Schoeffler EC, Fujita T, Nixon DF, Lanier LL. Tim-3 marks human natural killer cell maturation and suppresses cell-mediated cytotoxicity. Blood 2012;119:3734–3743.
81. Yu X, Harden K, C Gonzalez L, Francesco M, Chiang E, Irving B, Tom I, Ivelja S, Refino CJ, Clark H, Eaton D, Grogan JL. The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. Nat Immunol 2009; 10:48–57.
82. Bi J, Zheng X, Chen Y, Wei H, Sun R, Tian Z. TIGIT safeguards liver regeneration through regulating natural killer cell-hepatocyte crosstalk. Hepatology 2014; 60:1389–1398.
83. Saparbay J, Tanaka Y, Tanimine N, Ohira M, Ohdan H. Everolimus enhances TRAIL-mediated anti-tumor activity of liver resident natural killer cells in mice. Transpl Int 2020;33:229–243.
84. Ochi M, Ohdan H, Mitsuta H, Onoe T, Tokita D, Hara H, Ishiyama K, Zhou W, Tanaka Y, Asahara T. Liver NK cells expressing TRAIL are toxic against self hepatocytes in mice. Hepatology 2004;39:1321–1331.
85. Almasan A, Ashkenazi A. Apo2L/TRAIL: apoptosis signaling, biology, and potential for cancer therapy. Cytokine Growth Factor Rev 2003;14:337–348.
86. Radaeva S, Sun R, Jaruga B, Nguyen VT, Tian Z, Gao B. Natural killer cells ameliorate liver fibrosis by killing activated stellate cells in NKG2D-dependent and tumor necrosis factor–related apoptosis-inducing ligand–dependent manners. Gastroenterology 2006; 130:435–452.
87. Qi X, Li Z, Li H, Wang T, Zhang Y, Wang J. MicroRNA-1 negatively regulates peripheral NK cell function via tumor necrosis factor-like weak inducer of apoptosis (TWEAK) signaling pathways during PPRV infection. Front Immunol 2020;10:3066.
88. Exley MA, Koziel MJ. To be or not to be NKT: natural killer T cells in the liver. Hepatology 2004;40:1033–1040.
89. Bendelac A, Savage PB, Teyton L. The biology of NKT cells. Annu Rev Immunol 2007;25:297–336.
90. Kumar V. NKT-cell subsets: promoters and protectors in inflammatory liver disease. J Hepatol 2013; 59:618–620.
91. Brennan PJ, Brigl M, Brenner MB. Invariant natural killer T cells: an innate activation scheme linked to diverse effector functions. Nat Rev Immunol 2013;13:101–117.
92. Dong Z, Zhang J, Sun R, Wei H, Tian Z. Impairment of liver regeneration correlates with activated hepatic NKT cells in HBV transgenic mice. Hepatology 2007; 45:1400–1412.
93. Takeda K, Hayakawa Y, Van Kaer L, Matsuda H, Yagita H, Okumura K. Critical contribution of liver natural killer T cells to a murine model of hepatitis. Proc Natl Acad Sci 2000;97:5498–5503.
94. Friedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterology 2008;134:1655–1669.
95. Park O, Jeong WI, Wang L, Wang H, Lian ZX, Gershwin ME, Gao B. Diverse roles of invariant natural killer T cells in liver injury and fibrosis induced by carbon tetrachloride. Hepatology 2009;49:1683–1694.
96. Khawar MB, Azam F, Sheikh N, Abdul Mujeeb K. How does interleukin-22 mediate liver regeneration and prevent injury and fibrosis? J Immunol Res 2016;2016:1–8.
97. Liepelt A, Wehr A, Kohlhepp M, Mossanen JC, Kreggenwinkel K, Denecke B, Costa IG, Luedde T, Trautwein C, Tacke F. CXCR6 protects from inflammation and fibrosis in NEMOLPC-KO mice. Biochim Biophys Acta BBA - Mol Basis Dis 2019;1865:391–402.
98. Ben Ya'acov A, Meir H, Zolotaryova L, Ilan Y, Shteyer E. Impaired liver regeneration is associated with reduced cyclin B1 in natural killer T cell-deficient mice. BMC Gastroenterol 2017;17:44.
99. Thomas JA, Pope C, Wojtacha D, Robson AJ, Gordon-Walker TT, Hartland S, Ramachandran P, Van Deemter M, Hume DA, Iredale JP, Forbes SJ. Macrophage therapy for murine liver fibrosis recruits host effector cells improving fibrosis, regeneration, and function. Hepatology 2011;53:2003–2015.
100. Tacke F. Targeting hepatic macrophages to treat liver diseases. J Hepatol 2017;66:1300–1312.
101. Starkey Lewis PJ, Moroni F, Forbes SJ. Macrophages as a cell-based therapy for liver disease. Semin Liver Dis 2019;39:442–451.
102. Moore JK, Mackinnon AC, Wojtacha D, Pope C, Fraser AR, Burgoyne P, Bailey L, Pass C, Atkinson A, Mcgowan NWA, Manson L, Turner ML, Campbell JDM, Forbes SJ. Phenotypic and functional characterization of macrophages with therapeutic potential generated from human cirrhotic monocytes in a cohort study. Cytotherapy 2015;17:1604–1616.
103. Ma PF, Gao CC, Yi J, Zhao JL, Liang SQ, Zhao Y, Ye YC, Bai J, Zheng QJ, Dou KF, Han H, Qin HY. Cytotherapy with M1-polarized macrophages ameliorates liver fibrosis by modulating immune microenvironment in mice. J Hepatol 2017;67:770–779.
104. Baeck C, Wei X, Bartneck M, Fech V, Heymann F, Gassler N, Hittatiya K, Eulberg D, Luedde T, Trautwein C, Tacke F. Pharmacological inhibition of the chemokine C-C motif chemokine ligand 2 (monocyte chemoattractant protein 1) accelerates liver fibrosis regression by suppressing Ly-6C^{+} macrophage infiltration in mice. Hepatology 2014;59:1060–1072.
105. Li C, Zheng S, You H, Liu X, Lin M, Yang L, Li L. Sphingosine 1-phosphate (S1P)/S1P receptors are involved in human liver fibrosis by action on hepatic myofibroblasts motility. J Hepatol 2011;54:1205–1213.
106. Gomez-Muñoz A, Presa N, Gomez-Larrauri A, Rivera IG, Trueba M, Ordoñez M. Control of inflammatory responses by ceramide, sphingosine 1-phosphate and ceramide 1-phosphate. Prog Lipid Res 2016;61:51–62.
107. Yang L, Han Z, Tian L, Mai P, Zhang Y, Wang L, Li L. Sphingosine 1-phosphate receptor 2 and 3 mediate bone marrow-derived monocyte/macrophage motility in cholestatic liver injury in mice. Sci Rep 2015;5: 13423.
108. Yang J, Yang L, Tian L, Ji X, Yang L, Li L. Sphingosine 1-phosphate (S1P)/S1P receptor2/3 axis promotes

inflammatory M1 polarization of bone marrow-derived monocyte/macrophage via G(α)i/o/PI3K/JNK pathway. Cell Physiol Biochem 2018;49:1677–1693.

109. Hou L, Yang L, Chang N, Zhao X, Zhou X, Dong C, Liu F, Yang L, Li L. Macrophage sphingosine 1-phosphate receptor 2 blockade attenuates liver inflammation and fibrogenesis triggered by NLRP3 inflammasome. Front Immunol 2020;11:1149.
110. Ma WT, Jia YJ, Liu QZ, Yang YQ, Yang JB, Zhao ZB, Yang ZY, Shi QH, Ma HD, Gershwin ME, Lian ZX. Modulation of liver regeneration via myeloid PTEN deficiency. Cell Death Dis 2017;8, e2827–e2827.
111. Boukouaci W, Lauden L, Siewiera J, Dam N, Hocine HR, Khaznadar Z, Tamouza R, Borlado LR, Charron D, Jabrane-Ferrat N, Al-Daccak R. Natural killer cell crosstalk with allogeneic human cardiac-derived stem/progenitor cells controls persistence. Cardiovasc Res 2014;104:290–302.
112. Li L, Zeng Z, Qi Z, Wang X, Gao X, Wei H, Sun R, Tian Z. Natural killer cells-produced IFN-γ improves bone marrow-derived hepatocytes regeneration in murine liver failure model. Sci Rep 2015;5:13687.
113. Han QJ, Mu YL, Zhao HJ, Zhao RR, Guo QJ, Su YH, Zhang J. Fasudil prevents liver fibrosis via activating natural killer cells and suppressing hepatic stellate cells. World J Gastroenterol 2021;27:3581–3594.
114. Tosello-Trampont A, Surette FA, Ewald SE, Hahn YS. Immunoregulatory role of NK cells in tissue inflammation and regeneration. Front Immunol 2017;8.
115. Huang W, Dong Z, Wei H, Ding C, Sun R, Tian Z. Selective elimination of hepatic natural killer T cells with concanavalin A improves liver regeneration in mice. Liver Int 2006;26:339–345.
116. Wehr A, Baeck C, Heymann F, Niemietz PM, Hammerich L, Martin C, Zimmermann HW, Pack O, Gassler N, Hittatiya K, Ludwig A, Luedde T, Trautwein C, Tacke F. Chemokine receptor CXCR6-dependent hepatic NK T cell accumulation promotes inflammation and liver fibrosis. J Immunol 2013;190:5226–5236.
117. Schrumpf E, Tan C, Karlsen TH, Sponheim J, Björkström NK, Sundnes O, Alfsnes K, Kaser A, Jefferson DM, Ueno Y, Eide TJ, Haraldsen G, Zeissig S, Exley MA, Blumberg RS, Melum E. The biliary epithelium presents antigens to and activates natural killer T cells: autoimmune, cholestatic and biliary disease. Hepatology 2015;62:1249–1259.
118. Bandyopadhyay K, Marrero I, Kumar V. NKT cell subsets as key participants in liver physiology and pathology. Cell Mol Immunol 2016;13:337–346.
119. Wu X, Sun R, Chen Y, Zheng X, Bai L, Lian Z, Wei H, Tian Z. Oral ampicillin inhibits liver regeneration by breaking hepatic innate immune tolerance normally maintained by gut commensal bacteria. Hepatology 2015;62:253–264.
120. Martin-Murphy BV, Kominsky DJ, Orlicky DJ, Donohue TM, Ju C. Increased susceptibility of natural killer T-cell-deficient mice to acetaminophen-induced liver injury. Hepatology 2013;57:1575–1584.

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