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Editorial: Community series in hepatic immune response underlying liver cirrhosis and portal hypertension, volume II

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Editorial on the Research Topic

Community series in hepatic immune response underlying liver cirrhosis and portal hypertension, volume II

Introduction

The immune landscape of a healthy liver plays an important role in maintaining tissue homeostasis. However, when subjected to injury, such as metabolic disorders, alcohol consumption, hepatitis viruses infection, or autoimmune diseases, the hepatic immunologic equilibrium is impaired, leading to tissue inflammation and fibrosis and culminating with cirrhosis and liver cancer (Yi et al.; Zhang et al.) (1). Although the immune response during liver disease has received significant attention, the detailed mechanisms by which residual and infiltrating immune cells interact with the liver parenchyma and contribute to liver disease initiation and progression remain to be further explored.

This Research Topic includes 13 articles and reviews that focus on the role of immune response in different types of liver injury and summarize the current knowledge on liver immunology and pathophysiology, as well as emerging therapeutic targets.

Liver diseases and immune response

The immune response is a critical determinant in almost all kinds of liver diseases. Different types of immune cells actively participate in liver disease initiation and progression through various signaling pathways (Yi et al.; Zhang et al.) (2, 3). Several studies in this Research Topic have dissected distinct interactions between immune cells

and the liver to facilitate the understanding of the underlying mechanisms in different liver pathological settings.

Metabolic dysfunction-associated steatohepatitis

Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by hepatocyte steatosis, metabolic disorders, and dysregulated hepatic immune microenvironment (Zhang et al.). The growing burden of MASLD is partly attributed to the increasing prevalence of obesity and diabetes (4, 5). Sphingosine 1-phosphate (S1P) is a bioactive lipid released by stressed hepatocytes. The S1P receptor is expressed in a wide range of immune cells and, by binding S1P, can induce immune cell infiltration into the liver and contribute to liver inflammation and MASH progression (6, 7). The inhibitor of $S1P_1$, $S1P_4$, and $S1P_5$, etrasimod, showed a better effect than the single $S1P_1$ inhibitor in reducing the proportion of pro-inflammatory infiltrating immune cells and inducing the expression of anti-inflammatory markers on macrophages (Liao et al.). Liver injury and inflammation in the MASH mouse model are ameliorated after etrasimod treatment (Liao et al.). These results suggest a potential therapeutic opportunity utilizing S1P inhibitors in patients.

Chronic hepatitis B

Hepatitis B virus (HBV) infection is often chronic and difficult to eradicate because HBV can escape immune surveillance partly by impairing T-cell cytotoxic activity and cytokine production (8). $CD8^+$ T cells from chronic hepatitis B patients or $CD8^+$ T cells cocultured with hepatocytes infected with HBV have elevated expression of CD244, a regulator of immune functions (Xie et al.). Upregulation of lnc-AIFM2-1 and downregulation of miR-330-3p, two non-coding RNAs, induce the expression of CD244 on $CD8^+$ T cells, contributing to the exhaustion of $CD8^+$ T cells and subsequent HBV immune escape (Xie et al.). Non-coding RNAs have been indicated as potential contributors to liver diseases (9, 10). These findings further highlight the role of non-coding RNAs in the pathogenesis of chronic hepatitis B and propose novel therapeutic approaches by targeting HBV immune escape mechanisms.

Autoimmune liver diseases

Autoimmune liver diseases comprise autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and primary biliary cirrhosis (PBC), which are highly associated with aberrant hepatic immune responses. In AIH, pro-inflammatory tetraspanin 1^+ B cells are enriched in the liver and correlate with the severity of AIH. In addition, the CXCR3-CXCL10 pathway might be responsible for the recruitment of this B cell subgroup to the liver (Ou et al.). PBC and PSC are two major cholangiopathies where cholangiocyte functions are impaired. However, recent studies have unveiled a more active role of cholangiocytes in the pathogenesis of liver diseases. Cholangiocytes can dramatically switch their phenotype and secretory spectrum upon injury (Cai et al.). The soluble factors secreted by activated cholangiocytes, namely cholangiokines, have multifaceted effects on the liver, including the pro-regenerative, pro-inflammatory, pro-fibrotic, and pro-tumorigenic effects (11) (Cai et al.). The immune dysregulation affecting cholangiocytes is a key mechanism in PBC (Yang et al.). Nevertheless, the potential treatment options for PBC targeting the aberrant immune response are limited (12). Recently, encouraging results have been shown by targeting immune cells (such as the anti-CD20 monoclonal antibody rituximab targeting B cells) or chemokines (such as the dual CCR2/CCR5 inhibitor cenicriviroc) in patients with PBC or 2OA-BSA-induced PBC mouse models (Yang et al.) (13, 14). More clinical investigations are needed to evaluate the effect of novel therapies on autoimmune liver diseases.

Decompensated cirrhosis

Decompensated liver cirrhosis is the advanced stage of liver cirrhosis with impaired hepatic and systemic immune responses, including immunosuppression (15). In the relatively early stage of liver cirrhosis, the replication of torque teno virus, a marker of immunosuppression, is already observed in patients (Rueschenbaum et al.). Moreover, a drop in the number of lymphocytes and a decline in T cell functions are found in patients with decompensated cirrhosis, which predict the development of acute-on-chronic liver failure (ACLF) (Rueschenbaum et al.). After ACLF is developed, while the abovementioned immunophenotype changes remain, additional changes, including neutrophilia with characterized neutrophil phenotype and increased macrophage M0-like monocytes, appear and further contribute to immunosuppression during ACLF (Weiss et al.). In decompensated cirrhotic patients with sepsis, myeloid-derived suppressor cells expand and exacerbate immunosuppression by boosting FOXP3+ T regulator cells and downregulating $CD4^+$ T cell proliferation, which can be rescued by granulocyte-macrophage colony-stimulating factor (Sehgal et al.). Further studies are needed to understand the mechanism of immunosuppression during decompensated cirrhosis and explore novel therapeutic targets to prevent the progression toward ACLF.

Emerging therapeutic approaches and targets

As the study of the immune response in liver disease has received increasing interest, potential novel anti-fibrotic or anti-cirrhotic therapies that target the hepatic immune microenvironment are being developed (Zhang et al.) (16). With the advance of regenerative medicine, mesenchymal stem cell (MSC) therapy has emerged as a promising treatment option for liver cirrhosis. MSCs are pluripotent stem cells capable of differentiating and replenishing the liver parenchyma (17). MSCs

can also inhibit hepatic stellate cell activation and accelerate the degradation of extracellular matrix (Liu et al.; Yi et al.). Furthermore, the most appealing advantage of MSCs is that they can modulate the immune cell function through direct cell contact and paracrine signaling (including secretion of extracellular vesicles) (18, 19). MSCs can block the infiltration of pro-inflammatory immune cells while recruiting anti-inflammatory cells by secreting a wide spectrum of cytokines (Liu et al.; Yi et al.) (20, 21). Clinical trials have demonstrated promising outcomes of MSC therapy in patients with liver cirrhosis, showing benefits on the long-term survival rate and liver function (22, 23).

The gut-liver axis is another important area of investigation in the field of liver diseases. Gut-derived factors such as pathogen-associated molecular patterns, bile acids, and other metabolites can influence the composition of the liver immune microenvironment and contribute to liver disease progression (24, 25). Liver cirrhosis is often accompanied by gut microbiota dysbiosis, leading to the release of microbiota-specific factors. These factors can be sensed by Toll-like receptors (TLRs), a conserved family of pattern recognition receptors, triggering hepatic immune responses and influencing the progression of liver cirrhosis (Fan et al.). Targeting altered intestinal flora or TLRs, such as fecal microbial transplantation or inhibitors of TLR signaling, has been proposed as a potential treatment option for liver cirrhosis (Fan et al.) (26, 27). Some naturally occurring metabolites, such as neuropeptide galanin, also show a beneficial effect by alleviating liver inflammation and fibrosis in mice through modulating macrophage phenotype and function (He et al.). Further investigations are needed to identify the effect of these potential treatments in humans.

Conclusion

This Research Topic highlights the role of the hepatic immune response in the progression of liver diseases. Emerging therapeutic targets and approaches for liver cirrhosis have been reviewed and discussed. Nevertheless, given the substantial heterogeneity within the cirrhotic niche (28), further research is imperative to enhance our understanding of the pathological mechanisms and discover effective treatment approaches for liver cirrhosis.

Author contributions

TL: Writing – original draft, Writing – review & editing. SL: Writing – review & editing, Writing – original draft. HY: Writing – original draft, Writing – review & editing. EK: Writing – review & editing, Conceptualization, Funding acquisition, Supervision. JG: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

References

1. Kubes P, Jenne C. Immune responses in the liver. *Annu Rev Immunol* (2018) 36:247–77. doi: 10.1146/annurev-immunol-051116-052415

2. Hammerich L, Tacke F. Hepatic inflammatory responses in liver fibrosis. *Nat Rev Gastroenterol Hepatol* (2023) 20(10):633–46. doi: 10.1038/s41575-023-00807-x

3. Gao J, Wei B, Liu M, Hirsova P, Sehrawat TS, Cao S, et al. Endothelial P300 promotes portal hypertension and hepatic fibrosis through C-C motif chemokine ligand 2-mediated angiocrine signaling. *Hepatology* (2021) 73(6):2468–83. doi: 10.1002/hep.31617

4. Li J, Shi Q, Gao Q, Pan XF, Zhao L, He Y, et al. Obesity pandemic in China: epidemiology, burden, challenges, and opportunities. *Chin Med J (Engl)* (2022) 135 (11):1328–30. doi: 10.1097/cm9.0000000000002189

5. Shi Q, Nong K, Vandvik PO, Guyatt GH, Schnell O, Rydén L, et al. Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *Bmj* (2023) 381:e074068. doi: 10.1136/bmj-2022-074068

6. Park SJ, Im DS. Sphingosine 1-phosphate receptor modulators and drug discovery. *Biomol Ther (Seoul)* (2017) 25(1):80–90. doi: 10.4062/biomolther.2016.160

7. Mauer AS, Hirsova P, Maiers JL, Shah VH, Malhi H. Inhibition of sphingosine 1-phosphate signaling ameliorates murine nonalcoholic steatohepatitis. *Am J Physiol Gastrointest Liver Physiol* (2017) 312(3):G300–g13. doi: 10.1152/ajpgi.00222.2016

8. Ye B, Liu X, Li X, Kong H, Tian L, Chen Y. T-cell exhaustion in chronic hepatitis B infection: current knowledge and clinical significance. *Cell Death Dis* (2015) 6(3):e1694. doi: 10.1038/cddis.2015.42

9. Zhao C, Qian S, Tai Y, Guo Y, Tang C, Huang Z, et al. Proangiogenic role of circrna-007371 in liver fibrosis. *Cell Prolif* (2023) 56(6):e13432. doi: 10.1111/cpr.13432

10. Zeng X, Yuan X, Cai Q, Tang C, Gao J. Circular rna as an epigenetic regulator in chronic liver diseases. *Cells* (2021) 10(8):1945. doi: 10.3390/cells10081945

11. Lan T, Qian S, Tang C, Gao J. Role of immune cells in biliary repair. *Front Immunol* (2022) 13:866040. doi: 10.3389/fimmu.2022.866040

12. Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D, Vierling JM, Adams D, Alpini G, et al. The challenges of primary biliary cholangitis: what is new and what needs to be done. *J Autoimmun* (2019) 105:102328. doi: 10.1016/j.jaut.2019.102328

13. Myers RP, Swain MG, Lee SS, Shaheen AA, Burak KW. B-cell depletion with rituximab in patients with primary biliary cirrhosis refractory to ursodeoxycholic acid. *Am J Gastroenterol* (2013) 108(6):933–41. doi: 10.1038/ajg.2013.51

14. Reuveni D, Gore Y, Leung PSC, Lichter Y, Moshkovits I, Kaminitz A, et al. The critical role of chemokine (C-C motif) receptor 2-positive monocytes in autoimmune cholangitis. *Front Immunol* (2018) 9:1852. doi: 10.3389/fimmu.2018.01852

15. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol* (2014) 61(6):1385–96. doi: 10.1016/j.jhep.2014.08.010

16. Guo Y, Zhao C, Dai W, Wang B, Lai E, Xiao Y, et al. C-C motif chemokine receptor 2 inhibition reduces liver fibrosis by restoring the immune cell landscape. *Int J Biol Sci* (2023) 19(8):2572–87. doi: 10.7150/ijbs.83530

17. Lee KD, Kuo TK, Whang-Peng J, Chung YF, Lin CT, Chou SH, et al. *In vitro* hepatic differentiation of human mesenchymal stem cells. *Hepatology* (2004) 40(6):1275–84. doi: 10.1002/hep.20469

18. Yao L, Hu X, Dai K, Yuan M, Liu P, Zhang Q, et al. Mesenchymal stromal cells: promising treatment for liver cirrhosis. *Stem Cell Res Ther* (2022) 13(1):308. doi: 10.1186/s13287-022-03001-z

19. Kostallari E, Valainathan S, Biquard L, Shah VH, Rautou PE. Role of extracellular vesicles in liver diseases and their therapeutic potential. *Adv Drug Delivery Rev* (2021) 175:113816. doi: 10.1016/j.addr.2021.05.026

20. Zhang Y, Cai W, Huang Q, Gu Y, Shi Y, Huang J, et al. Mesenchymal stem cells alleviate bacteria-induced liver injury in mice by inducing regulatory dendritic cells. *Hepatology* (2014) 59(2):671–82. doi: 10.1002/hep.26670

21. Lee KC, Lin HC, Huang YH, Hung SC. Allo-transplantation of mesenchymal stem cells attenuates hepatic injury through il1ra dependent macrophage switch in a mouse model of liver disease. *J Hepatol* (2015) 63(6):1405–12. doi: 10.1016/j.jhep.2015.07.035

22. Shi M, Li YY, Xu RN, Meng FP, Yu SJ, Fu JL, et al. Mesenchymal stem cell therapy in decompensated liver cirrhosis: A long-term follow-up analysis of the randomized controlled clinical trial. *Hepatol Int* (2021) 15(6):1431–41. doi: 10.1007/s12072-021-10199-2

23. Liu Y, Dong Y, Wu X, Xu X, Niu J. The assessment of mesenchymal stem cells therapy in acute on chronic liver failure and chronic liver disease: A systematic review and meta-analysis of randomized controlled clinical trials. *Stem Cell Res Ther* (2022) 13(1):204. doi: 10.1186/s13287-022-02882-4

24. Guan H, Zhang X, Kuang M, Yu J. The gut-liver axis in immune remodeling of hepatic cirrhosis. *Front Immunol* (2022) 13:946628. doi: 10.3389/fimmu.2022.946628

25. Li B, Selmi C, Tang R, Gershwin ME, Ma X. The microbiome and autoimmunity: A paradigm from the gut-liver axis. *Cell Mol Immunol* (2018) 15(6):595–609. doi: 10.1038/cmi.2018.7

26. Okiyama W, Tanaka N, Nakajima T, Tanaka E, Kiyosawa K, Gonzalez FJ, et al. Polyenephosphatidylcholine prevents alcoholic liver disease in pparalpha-null mice through attenuation of increases in oxidative stress. *J Hepatol* (2009) 50(6):1236–46. doi: 10.1016/j.jhep.2009.01.025

27. Ma Z, Zhang E, Yang D, Lu M. Contribution of toll-like receptors to the control of hepatitis B virus infection by initiating antiviral innate responses and promoting specific adaptive immune responses. *Cell Mol Immunol* (2015) 12(3):273–82. doi: 10.1038/cmi.2014.112

28. Kostallari E, Wei B, Sicard D, Li J, Cooper SA, Gao J, et al. Stiffness is associated with hepatic stellate cell heterogeneity during liver fibrosis. *Am J Physiol Gastrointest Liver Physiol* (2022) 322(2):G234–g46. doi: 10.1152/ajpgi.00254.2021