EDITORIAL

From basic liver immunology to therapeutic opportunities for liver diseases

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Five years ago, we launched a special issue in the *Cellular & Molecular Immunology* with a focus on basic liver immunology, which included eight review articles covering the knowledge about immunological features of the liver.¹ To date, these articles have been cited more than 1200 times according to the Google Scholar. Over the past 5 years, enormous progress has been made in the understanding of liver immunology and the identification of various therapeutic strategies targeting inflammatory mediators for the diagnosis and treatment of liver diseases. Therefore, we are honored and excited to present another follow-up special issue to discuss the updated knowledge of translational liver immunology and the therapeutic targets based on the knowledge we learned from the studies of liver immunology.

In this special issue, first two papers discuss how gut microbiome and cytokines are involved in the development and progression of liver diseases. The follow-up three articles focus on the roles of several types of innate immune cells, such as neutrophils, macrophages, and innate lymphocytes, in the pathogenesis of liver diseases and the development of potential therapeutic targets. The immunological mechanisms of fatty liver disease, autoimmune liver disease (AILD), and hepatocellular carcinoma (HCC) are deliberated in the last three reviews.

The liver receives not only nutrients but also microbial products from the gut through hepatic portal vein system. For example, excessive gut derived bacterial components can directly interact with liver immune cells, especially Kupffer cells (KCs), thereby triggering inflammation in the liver.² How immune cells respond to signals coming from the gut and how the liver provides feedback to the gut via the bile acid secretion have been hot topics over the last several years, which are discussed by Wang et al.³ in this special issue. The authors also describe the signatures of gut microbiome in alcohol-associated liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), and AILD and how the alteration of gut microbiome contributes to the pathogenesis of these liver diseases. Finally, the authors provide insightful perspective for the intervention of liver diseases by rebuilding healthy gut microbiome.

Cytokines mediate the communication not only between immune cells but also between immune cells and nonimmune cells. In the liver, cytokines are involved in the initialization, progression, and resolution of all types of liver diseases. In this special issue, He et al.⁴ summarize how interferons, helper T-cell cytokines, IL-1 family cytokines, IL-6 family cytokines, and IL-20 family cytokines regulate liver injury, inflammation, fibrosis, and regeneration. They also deliberate the functions of numerous hepatocyte-derived cytokines. Finally, several cytokines, that are currently being examined as potential therapeutic agents or therapeutic targets for liver diseases, are also discussed in this review. Particularly, a recent Phase IIb trial reported promising results of IL-22 therapy for patients with severe alcoholic hepatitis.⁵ Recent studies from preclinical models suggest that IL-22 has also great therapeutic potential for the treatment of acute-on-chronic liver failure⁶ and nonalcoholic steatohepatitis (NASH).⁷

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Innate immune cells, such as neutrophils, macrophages, and innate lymphocytes, have been shown to play important roles in the pathogenesis of liver diseases, which are discussed in three review articles in this special issue. Therapeutic opportunities targeting these cells are also deliberated. Neutrophils usually stay in peripheral blood and bone marrow in healthy subjects, but they can be rapidly mobilized into the liver in response to hepatocyte damage caused by alcohol intake, lipid accumulation, or other hepatotoxins. Neutrophil infiltration has been observed in all types of liver diseases and is a hallmark of steatohepatitis. In this special issue, Liu et al.⁸ summarize the behavior of neutrophils in various types of liver diseases including viral hepatitis, NAFLD, ALD, liver fibrosis, liver failure, and HCC. The mechanisms of protective and harmful roles of neutrophils played in liver diseases are also extensively discussed.

Macrophages, another type of abundant myeloid cells in the liver, have been well studied in many types of liver diseases. Live macrophages, which include both liver resident KCs and monocyte-derived macrophages, not only are critical in maintaining homeostasis of the liver but also contribute to the development of liver injury and regeneration. As a heterogeneous population of cells, liver macrophages have been reported to play diverse or contradictory roles in the pathogenesis of liver diseases in different studies.⁹ In the previous special issue of Basic Liver Immunology, Drs. Ju and Tacke¹⁰ comprehensively deliberated liver macrophages in homeostasis and liver diseases: from pathogenesis to novel therapeutic strategies. In the current issue, Wen et al.¹¹ provide an update on the studies on the origin, function, and plasticity of hepatic macrophages, which is very helpful to clarify the complex roles of macrophages in the liver under both physiological and pathological conditions. In addition, the authors also include the summary of how to target macrophages as a therapeutic strategy for the treatment of NASH in patients.

As an organ processes a large amount of bacterial products, environmental toxins, and food antigens from gut, the liver is enriched with innate lymphocytes such as natural killer (NK) cells, NKT cells, $\gamma\delta$ T cells, mucosal-associated invariant T cells and groups 1, 2, and 3 innate lymphoid cells. These cells are critical for the liver to fight against viral infection and surveil tumor growth. Among these innate immune cells, liver NK cells have been best characterized and were discussed in the previous special issue.¹² In the current issue, Chen et al.¹³ provide recent progress on the studies of subsets of innate lymphocytes in the liver, especially the discovery of liver resident NK cells. They deliberate the functions of innate lymphocytes in liver diseases including ALD, NAFLD, AILD, and liver cancer. In addition, new therapeutic approaches targeting NK cells for HCC and NASH are also mentioned in this review.

The last three review articles focus on the immunological mechanisms of three types of liver diseases including fatty liver diseases, AILD, and HCC. As the two major types of chronic liver diseases, ALD and NAFLD are associated with inflammatory responses that are critical for the disease development and progression. Over the last two decades, the immunological mechanisms for the pathogenesis of ALD and NAFLD have been extensively investigated, which are summarized by Wang et al.¹⁴ in the current issue. Particularly, they provide the discussion on how immune cells and inflammatory factors contribute to the progression of alcoholic steatohepatitis and NASH. Inflammatory targets for the treatment of both maladies are also summarized in this review.

AILD includes autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis. These diseases share common features of massive lymphocyte infiltration and elevated auto-antibodies. Although the exact causes for AILD remain elusive, disruption of immune tolerance to self-antigens may be the most

important risk factor for the development AILD. Horst et al.¹⁵ summarize the emerging knowledge about antigen presentation in the liver by professional antigen-presenting cells (APCs), such as dendritic cells and macrophages, as well as nonprofessional APCs like liver sinusoidal endothelial cells, hepatic stellate cells, cholangiocytes, and hepatocytes. The mechanisms of autoantibody generation in AILD and novel therapeutic approaches for AILD are also included in this review.

Over the last several years, enormous progress has been made in the immunotherapy for many types of cancers. Treatment with immune checkpoint inhibitors such as PD1/PDL1 blocking antibodies has been reported to significantly improve the survival of patients with several types of cancers.¹⁶ However, the efficacy of immunotherapy for HCC is less satisfactory.¹⁷ One possible explanation is that the immune microenvironment in the liver is unique. As we discussed above, the liver is an immunological organ with abundant innate and innate-like immune cells. The behavior of these cells may directly or indirectly impact the immunotherapy of HCC. In this special issue, Ruf et al.¹⁸ summarize the roles of innate and innate-like immune cells in liver cancer. Based on the understanding of immunobiology of HCC, the authors also update the current immunotherapies for HCC and propose future direction of the immune-based HCC therapy.

Liver immunology was the central focus of research in the field of viral hepatitis in the past due to its important role in the control of hepatitis virus replication and in the exploration of therapeutic targets for the treatment. Since the effective direct-acting antiviral drugs and nucleos(t)ide analogs were discovered for the treatment of patients with chronic viral hepatitis, liver immunology research on viral hepatitis has been received less attention, but this is still an important topic, which is not discussed in this special issue due to space limitations.

In summary, liver inflammation plays key roles in the pathogenesis of liver diseases, thus targeting inflammation may have therapeutic potential for several types of liver diseases, especially for the ALD, NASH, AILD, and HCC treatment. We hope this special issue will help us better understand translational and clinical liver immunology, thereby finding better strategies for the diagnosis and treatment of liver diseases.

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ADDITIONAL INFORMATION

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