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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Innate Lymphoid Cells: New Culprits of Alcohol-Associated Steatohepatitis

Over the past decades, the increase in alcohol-associated liver disease (ALD)-related morbidity and mortality has spurred efforts to understand the underlying mechanisms of ALD. Many early studies reported critical roles of Kupffer cells and Toll-like receptor 4 activation in the pathogenesis of ALD, which results in proinflammatory cytokine production and infiltration of macrophages and neutrophils.[1] However, a recent study identified a large number of inflammatory cells in severe alcoholic hepatitis that included various types of lymphocytes.[2] Nevertheless, the exact roles of these lymphocytes and the cytokines they produce in the development of alcohol-associated steatohepatitis are yet to be elucidated clearly. Of the numerous cytokines, interleukin (IL)-17, which is produced by $CD4^+$ T helper 17 (Th17) cells, hepatic macrophages, and $\gamma\delta$ T cells, stimulates inflammatory responses, including neutrophil migration, and triggers the onset of hepatic fibrosis.[3-5] IL-17-producing Th17 cells differentiate from naive T cells through transforming growth factor-β1 and IL-6-mediated transcriptional regulation of RORγt, whereas hepatic macrophages and $\gamma\delta$ T cells produce IL-17 after activation of TLR9 and TLR3 following exosomal delivery of mitochondrial DNA or mitochondrial double-stranded RNA. Aside from these cell types, innate lymphoid cells are also known to produce IL-17.[6] Innate lymphoid cells belong to a family of innate immune cells and are largely equivalent to T cells, except that they do not express acquired antigen receptors, such as T and B cells.[6,7] Innate lymphoid cells consist of 3 groups, where group 1 innate lymphoid cell encompasses cytotoxic natural killer (NK) cells and type 1 innate lymphoid cell (ILC1), with both cell types enriched in the healthy liver of mice at a roughly 1:1 ratio.[7] Although ILC1 and NK cells share several functional properties, including cytokine production, they differ in developmental pathways and cytotoxicity.[6,7] With recently growing interest in innate lymphoid cells, the roles of ILC1 and NK cells in various liver diseases, including nonalcoholic steatohepatitis and cancer, have previously been investigated.[7] However, the question remains as to whether the interaction between ILC1 and NK cells is critical in ALD as well.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Cheng et al[8] provide an important insight into understanding the pathophysiology of alcohol-associated steatohepatitis. They suggest that the dysfunctional interplay between hepatic ILC1 and NK cells results in highly elevated levels of IL-17, promoting the progression of alcohol-associated steatohepatitis. The authors first identify $TRAIL^+CD69^+CD49a^+$ ILC1 as the dominant cell type in group I innate lymphoid cells, because most NK cells undergo apoptosis in the murine model of alcohol-associated steatohepatitis. When they performed adoptive transfer of $CD49b^+$ NK cells or polyriboinosinic polyribocytidylic acid (poly I:C)-mediated NK cell expansion in the liver, alcohol-associated steatohepatitis was significantly attenuated as indicated by decreased serum levels of hepatic triglyceride, alanine aminotransferase, and aspartate aminotransferase. In addition, mRNA expression of IL-6 and IL-1β in the liver tissues was reduced with restored NK cells. Similarly, as they depleted ILC1, symptoms of hepatitis were ameliorated along with a conspicuous decrease in neutrophil infiltration, suggesting that hepatic NK cells may have a protective role against alcohol-associated steatohepatitis by repressing the activation of ILC1 cells. The authors then demonstrate that ILC1 cells contribute to alcohol-associated steatohepatitis by producing IL-17A because neutralizing IL-17A reversed disease progression in the Gao-Binge alcohol consumption model. On a side note, several previous studies had reported the production of IL-17A in ALD.[3,5] Thus, a single ethanol binge increased IL-1β and IL-23 production of Kupffer cells through hepatic exosomal delivery of mitochondrial double-stranded RNA to TLR3, thereby stimulating IL-17A production and migration of $\gamma\delta$ T cells without T-cell receptor engagement in acute alcoholic inflammation.[5] In addition, in the model of intragastric ethanol ingestion plus Western diet feeding, hepatocyte-derived extracellular vesicles were enriched with mtDNA, and their delivery to hepatic macrophages stimulated IL-17A production in a TLR9-dependent manner.[3] The authors' investigation demonstrated that normalization of the ILC1/NK cells ratio induced significant attenuation of alcohol-induced steatohepatitis. As hepatic interferon-γ levels were increased by restoring or expanding NK cell population (adoptive transfer or poly I:C-induced stimulation), IL-17A production by ILC1 was inhibited, thereby attenuating alcohol-associated steatohepatitis. In parallel with this finding, a significant decrease in hepatic NK cells accelerated alcohol-induced liver fibrosis in mice.[9] All these findings suggested that interferon-γ production of NK cells may be crucial in alleviating the alcohol-induced steatohepatitis and liver fibrosis as well.

In conclusion, the authors in this *Cellular and Molecular Gastroenterology and Hepatology* article propose a new potential therapeutic target for alcohol-associated steatohepatitis that centers on the interaction between ILC1 and NK cells. This study is notable because it delves into the involvement of hepatic lymphocytes in the pathogenesis of ALD, which has not received much attention thus far. Despite its novel findings, this study did not identify the major cell type that produces IL-17A in alcohol-associated

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steatohepatitis and the underlying mechanism of IL-17A production in ILC1 cells. In fact, identifying the major IL-17-producing cell type in patients could be challenging because diverse hepatic nonparenchymal cells can produce IL-17, which vary in abundance depending on the disease severity. Additionally, clinical application of the current findings, such as transferring autologous or homologous NK cells or chemically stimulating the expansion of hepatic NK cells in patients with ALD, requires further investigation.

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