XCR1⁺ type 1 conventional dendritic cells drive liver pathology in non-alcoholic steatohepatitis

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Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are prevalent liver conditions that underlie the development of life-threatening cirrhosis, liver failure and liver cancer. Chronic necro-inflammation is a critical factor in development of NASH, yet the cellular and molecular mechanisms of immune dysregulation in this disease are poorly understood. Here, using single-cell transcriptomic analysis, we comprehensively profiled the immune composition of the mouse liver during NASH. We identified a significant pathology-associated increase in hepatic conventional dendritic cells (cDCs) and further defined their source as NASH-induced boost in cycling of cDC progenitors in the bone marrow. Analysis of blood and liver from patients on the NAFLD/NASH spectrum showed that type 1 cDCs (cDC1) were more abundant and activated in disease. Sequencing of physically interacting cDC-T cell pairs from liver-draining lymph nodes revealed that cDCs in NASH promote inflammatory T cell reprogramming, previously associated with NASH worsening. Finally, depletion of cDC1 in XCR1^{DTA} mice or using anti-XCL1-blocking antibody attenuated liver pathology in NASH mouse models. Overall, our study provides a comprehensive characterization of cDC biology in NASH and identifies XCR1⁺ cDC1 as an important driver of liver pathology.

NAFLD, a hepatic manifestation of metabolic syndrome, is present in 25% of the population globally. Up to 40% of individuals with NAFLD develop NASH, involving chronic inflammation and fibrosis associated with life-threatening cirrhosis and hepatocellular carcinoma, as well as non-liver-associated adverse outcomes such as type 2 diabetes and cardiovascular disease[1–3]. NAFLD/NASH has become the most common cause of chronic liver disease worldwide and will soon overtake hepatitis C virus as the leading cause of liver transplantation[1]. Mechanistically, NAFLD starts with progressive hepatic steatosis, manifested by the presence of enlarged lipid droplets in hepatocytes. Chronic fat overload induces endoplasmic reticulum stress, mitochondrial stress, aberrant hepatocyte metabolism and subsequent hepatocyte death, resulting in release of various danger signals, which trigger immune infiltration, lobular and portal inflammation, compensatory proliferation and in a chronic unresolved state, fibrosis[1,4]. Currently there is no efficient treatment to address NAFLD/NASH, except lifestyle modifications leading to weight reduction; a recommendation followed with little adherence[4,5].

The liver is the main organ responsible for metabolic and detoxification processes, but also acts as a frontline immune tissue. The liver is strategically positioned to interact with foreign antigens entering the body from the gut via the portal vein[6]. These include microbial products, toxins and food-derived antigens. To sense and respond to such complex stimuli in an appropriate manner, the liver is populated by a wide variety of immune cells and their composition changes significantly in response to infection or injury[7].

Systemic inflammation accompanying metabolic syndrome in general and hepatic immune composition in particular, was implicated in regulating different modalities of NAFLD and NASH. Mice lacking CD8⁺ T cells are protected against multiple facets of metabolic syndrome, including development of NASH[8–13], while another study showed that type 2 immunity negatively affects the liver in NASH, despite its protective effects in the adipose tissue[14]. Triggering receptor expressed on myeloid cells 2 (TREM2)⁺ macrophages accumulate in the liver with NAFLD[15,16] and NASH[17] and were suggested to limit liver damage in mice[18] but promote liver fibrosis in humans[19]. Although much progress has been made in

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