Editorial

The role of B cells in metabolic (dysfunction)-associated fatty liver disease

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Metabolic (dysfunction)-associated fatty liver disease (MAFLD; formerly known as non-alcoholic fatty liver disease) is the most common liver disorder, affecting around one-third of the population worldwide (1). MAFLD is a heterogeneous disease with a spectrum of liver pathologies that spans from hepatic lipid accumulation (steatosis) to chronic inflammation (steatohepatitis), which can progress to cirrhosis and hepatocellular carcinoma. It is impacted by a myriad of factors, including metabolic health, biological and chronological age, genetics and epigenetics (2-4). However, only a proportion (5–40%) of patients develop liver inflammation or steatohepatitis (5). This transition is a cardinal feature of progressive liver disease, which is the precursor to the development of the hepatic and extra-hepatic outcomes.

Notably, the unique anatomical structure and position of the liver, where immune cells encounter antigen-rich blood from the gastrointestinal tract, have rendered it to be considered as an immunological organ. The recruitment and migration of immune and pro-inflammatory cells into the liver, which subsequently profoundly shapes the immunological response of the liver, is a crucial event in the initiation and progression of the critical transition to steatohepatitis (6). In this complex microenvironment, innate immune mechanisms, which include the activation of resident Kupffer cells and recruitment of leukocytes that release inflammatory mediators and contribute to the inflammatory response, have long been thought as the main contributing factor to the progression to steatohepatitis (6). However, emerging evidence suggests that adaptive immunity could play a pivotal role in this process. As B lymphocytes produce cytokines and antibodies, with recent evidence suggests their crucial role in promoting inflammation and the progression of MAFLD, although this remains to be fully characterised.

In a recent elegant study, Barrow *et al.* (7) provided novel insights into this role of B lymphocytes. In their work, they suggested a pivotal role of B cells as well as the communication between B cells and other intra-hepatic both immune and non-immune cells in the progression of MAFLD. They found that B cells are among the most abundant immune cells in the liver and are strong inducers of T-cell responses during the progression of steatohepatitis. They demonstrated that B-cell depletion led to a net effect of resolution of steatohepatitis, while adoptively transferring B cells from NASH livers caused disease recurrence, suggesting that B-cell activation in the liver is a causative factor rather than a bystander in the pathogenesis of steatohepatitis.

Broadly, according to the expressions of cell-surface markers, B cells can be classified into two subsets (B1 and B2). B1 cells arise from the foetal liver, while B2 cells derive from haematopoietic progenitors in the bone marrow (8). Barrow *et al.* (7) reported that high-fat high-carbohydrate diet-fed mice that mimicked various features of human steatohepatitis demonstrated an enhanced prevalence of B2 cells and a decreased percentage of B1b cells compared with normal chow diet-fed mice. In mice with steatohepatitis, this B cell response is accompanied by the upregulation of hepatic expression of B cell-activating factor (BAFF), one of

the cytokines that promotes B cell survival and maturation (9). Interestingly, circulating levels of BAFF has been shown to be higher in patients with steatohepatitis than in those with simple steatosis, and the levels correlated with the severity of steatohepatitis and fibrosis (10).

The pro-inflammatory and fibrogenic roles of B cells in MAFLD involve their interaction with other immune and non-immune hepatic cells. Barrow *et al.* (7) reported that B cells secrete fewer inflammatory cytokines than macrophages and neutrophils on a per-cell basis. They found that B cells in steatohepatitis livers stimulate the generation of CD4 and CD8 T cells, which promote inflammatory response. In addition, these inflammatory mediators might be implicated in the activation of hepatic stellate cells and liver macrophages. Of note, Barrow *et al.* (7) observed that intra-hepatic, but not splenic, B cells stimulate type 1 T-helper (Th1) responses. As indicated by the authors, these findings suggest that the B-cell acquisition of the pro-inflammatory phenotype is likely secondary to local activation rather than a systemic inflammatory response.

In both human and murine models, the 'Western' diet has been found to induce alterations in the gut flora and intestinal permeability, which lead to increased circulating levels of antigen-rich bacterial products. Subsequent intra-hepatic activation of pattern recognition receptors, including toll-like receptors, a sensor for these products, is a pivotal event in the initiation of steatohepatitis (6). Differential gut microbiota between subtypes of MAFLD has been suggested (11). Barrow *et al.* (7) also reported that the mechanisms of B-cell activation include gut-derived microbial antigens that may serve as ligands that activate intra-hepatic B cells during steatohepatitis. They also suggested that B-cell activation during steatohepatitis can occur simultaneously through the innate adapter myeloid differentiation factor 88 (MyD88) signalling, which leads to the stimulation of the nuclear factor κB and B-cell receptor (BCR) signalling pathways. This was based on the finding that B cell-specific deletion of MyD88 ameliorated hepatic T cell-mediated inflammation and fibrosis (7).

As is typical in science, this work raises some other questions and stimulates further directions. Future research is needed to identify additional critical contextual mechanisms, both antigen dependent and independent, for the activation of intra-hepatic B cells and enhancing the progression to steatohepatitis. In addition, identification of B-cell-directed therapies can be an attractive therapeutic avenue. Various strategies may be employed to achieve this goal including B-cell depletion, suppression of B-cell survival and proliferation, attenuation of the interaction between T and B cells and modulation of B-cell downstream inflammatory mediators or BCR signalling pathways (12). However, untargeted side effects, including toxicity and immunosuppression, may be a concern. Therefore, further preclinical evidence, including the delineation of the differential role of various B-cell subsets in the pathogenesis of MAFLD, is needed to guide the development of more-selective strategies in targeting the B-cell signalling pathway for the treatment of MAFLD.

In summary, the study by Barrow *et al.* (7) highlights that B cells are an emerging central player in MAFLD progression. This finding provides interesting novel clues into the role of immune cells in the pathogenesis of the disease and therefore represents a new avenue for the potential effectiveness of B-cell-specific therapeutic strategies.

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