Macrophages in obesity and non-alcoholic fatty liver disease: Crosstalk with metabolism

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Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease worldwide, and a major cause of liver cirrhosis and hepatocellular carcinoma. NAFLD is intimately linked with other metabolic disorders characterized by insulin resistance. Metabolic diseases are driven by chronic inflammatory processes, in which macrophages perform essential roles. The polarization status of macrophages is itself influenced by metabolic stimuli such as fatty acids, which in turn affect the progression of metabolic dysfunction at multiple disease stages and in various tissues. For instance, adipose tissue macrophages respond to obesity, adipocyte stress and dietary factors by a specific metabolic and inflammatory programme that stimulates disease progression locally and in the liver. Kupffer cells and monocyte-derived macrophages represent ontologically distinct hepatic macrophage populations that perform a range of metabolic functions. These macrophages integrate signals from the gut-liver axis (related to dysbiosis, reduced intestinal barrier integrity, endotoxemia), from overnutrition, from systemic low-grade inflammation and from the local environment of a steatotic liver. This makes them central players in the progression of NAFLD to steatohepatitis (non-alcoholic steatohepatitis or NASH) and fibrosis. Moreover, the particular involvement of Kupffer cells in lipid metabolism, as well as the inflammatory activation of hepatic macrophages, may pathogenically link NAFLD/NASH and cardiovascular disease. State-of-the art technologies, particularly single-cell RNA sequencing, spatial transcriptomics / proteomics and intravital microscopy, identified heterogeneous myeloid cell subsets in NAFLD mouse models and human liver, and tremendously advanced our understanding on diverse roles of macrophages in disease progression or regression in the liver. Evidence from animal and clinical studies suggests that macrophage targeting may improve the course of NAFLD and related metabolic disorders.