Unique Response of Liver Cells to Concanavalin A-Induced Immunohepatitis

In many cases, idiopathic drug-induced liver injury (IDILI) has an underlying immunopathological component, characterized by lymphocytes adhering to an inflamed liver sinusoid and causing acute hepatitis. Targeted intervention for IDILI requires understanding cell type-specific responses. The objective of this study was to dissect the immune system-related response of liver sinusoidal endothelial cells (LSEC), Kupffer cells (KC), infiltrating myeloid cells (MC), and the liver as a whole during acute intrahepatic immune infiltration. Concanavalin A (ConA), a plant lectin, models T-cell-mediated liver damage when administered intravenously (iv) to mice. C57BL/6J mice (4/group) were administered low-dose ConA (5 mg/kg, iv) or PBS. Liver tissue and purified liver cells were isolated at 4 and 24 hours following treatment using liver perfusion and flow cytometry sort-purification, then analyzed with microfluidic qRT-PCR for expression of genes associated with inflammatory, suppressive, or repair phenotypes. Low-dose ConA treatment induced rapid intrahepatic accumulation of lymphocytes and myeloid cells, but minimal increase in serum alanine aminotransferase. Cells from control mice demonstrated the basal immunosuppressive nature of KC, with notable expression of IL-10, and expression of antigen presentation molecules Cd80, Cd86, and H2-Aa (encoding MHC-II). As lymphocytes accumulated at 4 hours post-treatment, LSEC showed marked induction of the cell adhesion molecules Vcam1 and Icam1, while KC suppressed IL-10 and induced Nos2, Tnf, IL-12b, IL-6, Ifng, and IL-1a. Infiltrating MC showed a similar response to resident KC. Unexpectedly, the liver (i.e., primarily hepatocytes) induced strong expression of Nos2 and suppressed Arg1. By 24 hours, expression of most genes returned to basal levels, with the exception of robust induction of collagen genes (Col1a1 and Col3a1) in the liver as a whole. These results illustrate the rapid kinetics of immunopathology and highlight the unique roles of LSEC, macrophages, and hepatocytes during intrahepatic immunopathology.