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2) Lay summary

The effects of regulatory T cells and dendritic cells on progression of bile duct injury in mdr2 knockout mice, a mouse model of PSC, are unknown. In our experiments using antibodies and cytokines to change the number and function of these cells in the liver of these mice we found that regulatory T cells dampen immune-mediated liver injury: when these cells are removed from the liver, the disease worsens, if these cells are increased in number, the liver is protected. Similarly, when we blocked the function of dendritic cells we reduced the activation of T lymphocytes and protected liver cells from injury. In order to understand how these inflammatory processes in the liver are affected by bile acids, which are retained in the liver in PSC, we blocked reuptake of bile acids in the intestine using a small molecule compound. This treatment greatly reduced serum bile acid-, ALT- and alkaline phosphatase levels, and diminished liver fibrosis (scarring). Importantly, these changes were associated with down regulation of genes driving liver inflammation. In a translational study we reviewed clinical course, liver biopsies and MRI studies from 50 children and young adults who received care for PSC at our center. We found that their type of liver disease was dependent on the type of concomitant bowel disease (Crohn disease, Ulcerative colitis, or no IBD). Our next studies will aim to find out how the gut-liver axis shapes the inflammatory responses in the liver and how this inflammation can be safely treated to hold progression of PSC.