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Dysregulated bile transporters and impaired tight junctions promote chronic liver injury in mice

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Liver fibrosis, hepatocellular necrosis, inflammation and proliferation of liver progenitor cells are the hallmarks of chronic liver injury. Several murine models have been used to mimic the pathophysiology of chronic liver injury. However, the underlying differences in the molecular mechanism driving liver injury in different models remains largely unknown due to our inability to visualize the progression of liver injury *in vivo* in mice. Here, we use intravital imaging of bile transport and blood-bile barrier integrity in the intact liver of live mice. We show for the first time that breach of blood-bile barrier and impairment of bile secretion promotes choline-deficient-ethionine-supplemented (CDE) and 3, 5-diethoxycarbonyl-1, 4-dihydrocollidine (DDC) diets induced chronic liver injury in mice. The impairment in bile secretion was associated with the disruption of the blood-bile barrier, differential expression of several tight junction adhesion molecules and loss of bile transporters. Surprisingly, the prolonged use of CDE diet led to reappearance of tight junction adhesion molecules as well as bile transporters, which was concomitant to the reestablishment of blood-bile barrier integrity and rescue of bile secretion. Our findings demonstrate the potential of intravital imaging in elucidating the underlying pathophysiology in mice models of chronic liver injury and identify the loss of bile transporters or tight junction adhesion molecules as two distinct mechanisms contributing to progression of chronic liver injury.