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Hepatocyte specific ablation of β and γ -catenin leads to altered hepatocyte polarity and microvillae association

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Liver is the largest organ in a vertebrate body which is structurally and functionally complex and is considered second to the brain in its complexity. It is highly heterogeneous in nature and consists of various cell types. Hepatocytes are the predominant type of cells present in liver which is responsible for its many important functions including bile production, detoxification, cholesterol synthesis etc. Like any other epithelial cell, hepatocytes are polarized towards the apico-basal axes. Polarization of hepatocytes is necessary for many functions and requires carefully orchestrated cooperation between cell adhesion molecules, extracellular matrix, cell junctions, cytoskeleton, and intracellular trafficking machinery. Loss of hepatocyte polarity is associated with various liver diseases including cholestasis.

Recently, we have shown that absence of adherent junctional protein β and γ catenin in the liver leads to cholestatic liver disease. However, the molecular mechanism that leads to cholestasis in the absence of β - γ -catenin is not known. Therefore, we developed a hepatocyte specific conditional knockout of β and γ catenin to further characterize their role in this disease. TEM and SEM analysis of β - γ -catenin knockout liver showed aberrant tight junctional and adherent junctional structures. Permeability assay confirmed that barrier function of tight junctions is completely lost in these mice resulting in mixing of the bile with the blood. We also found that bile canaliculi, which is apically located in hepatocytes designated for bile storage is strongly dilated with significant reduction in microvilli inside them. Further analysis revealed that loss of β - γ -catenin leads to reduced expression of HNF4 α target genes. Remarkably, we found that loss of HNF4 α phenocopies β - γ -catenin knockout liver causing aberrant tight and adherent junctional structure. Studies designed to address the molecular mechanism behind the regulation of β ; γ -catenin in maintaining hepatocyte polarity and association of β ; γ -catenin and HNF4 α in promoting hepatocyte polarity are currently underway. Profound understanding of the regulation of hepatocyte polarity by both β -and γ - catenin will be useful in the context of liver development and pathophysiology.