Abstract

This thesis investigates the crucial role of plectin, a versatile cytolinker protein, in maintaining the structural integrity and function of liver epithelial cells, specifically hepatocytes and bile duct cells (BEC). Plectin's interactions with keratin filaments and cell adhesion structures such as desmosomes are essential for the stability and resilience of the liver under both physiological and pathological conditions. In our study, we used a liver-specific plectin knockout mouse model ($Ple^{\Delta alb}$) to explore the effects of plectin deficiency on liver cytoarchitecture and the liver's response to cholestatic injury. Immunofluorescence and electron microscopy revealed that plectin-deficient hepatocytes exhibited disrupted keratin networks, with a loss of the typical peri-membranous distribution and increased bundling of keratin filaments within the cytoplasm. This altered cytoarchitecture was associated with significant bile canaliculi dysmorphology, including wider, more meandering bile canaliculi with frequent blind end loops, which are indicative of impaired bile flow and increased biliary pressure. Similarly, BECs in $Ple^{\Delta alb}$ mice showed apicobasal redistribution of keratin filaments and dysregulated cell-cell adhesions, including shorter tight junctions and elevated expression of E-Cadherin. Despite these cytoarchitectural changes, untreated $Ple^{\Delta alb}$ mice did not display significant liver pathology or defects in bile secretion under basal conditions. However, under cholestatic stress induced by bile duct ligation (BDL), 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) feeding, and cholic acid (CA) feeding, $Ple^{\Delta alb}$ mice exhibited significantly aggravated liver injury compared to control mice. This was characterized by more severe biliary epithelial damage, increased fibrosis, and an exacerbated ductular reaction, particularly in the BDL and CA models. Interestingly, the study also demonstrated that the cholestatic stress response in $Ple^{\Delta alb}$ mice involved an adaptive remodeling of the biliary tree, with increased intraluminal surface area through corrugation, potentially as a compensatory mechanism to alleviate cholestatic injury. However, the inability of plectin-deficient cells to efficiently upregulate bile acid transporters and maintain cytoskeletal integrity under stress highlighted the critical role of plectin in preserving liver function. Overall, the findings of this thesis underscore the importance of plectin in maintaining liver epithelial cell integrity, particularly in the face of cholestatic challenges.