論文の内容の要旨

The transcription factor Klf5 is essential for intrahepatic biliary epithelial tissue remodeling against liver injury

(転写因子 Krüppel-like factor 5 による
肝障害時における肝内胆管の適応的リモデリング)

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Under various conditions of liver injury, the intrahepatic biliary epithelium undergoes dynamic tissue expansion and remodeling, a process known as ductular reaction. Mouse genetic models defective in inducing such a tissue remodeling process are more susceptible to liver injury, suggesting its crucial role in liver regeneration. However, the molecular mechanisms regulating the biliary epithelial cell (BEC) dynamics in ductular reaction remain largely unclear. Here, we demonstrated that the transcription factor Krüppel-like factor 5 (Klf5) is highly enriched in mouse liver BECs and it plays a key role in regulating the ductular reaction, specifically under cholestatic injury conditions. Although mice lacking Klf5 in the entire liver epithelium, including both hepatocytes and BECs (Klf5 LKO mice), did not exhibit any apparent phenotype in the hepatobiliary system under normal conditions, they exhibited significant defect in biliary epithelial tissue remodeling upon 3,5-diethoxycarbonyl-1,4-dihydrocollidine-induced cholangitis, concomitantly with exacerbated cholestasis and reduced survival rate. In contrast, mice lacking Klf5 solely in hepatocytes did not exhibit any comparable phenotype, confirming its specific role in BECs. Transcriptome analyses of BECs isolated from the Klf5 LKO

mouse liver revealed that expression of cell cycle-related genes was primarily affected. Accordingly, immunostaining analysis using Ki67 showed that the level of BEC proliferation upon injury was significantly reduced in the Klf5 LKO mice. These results indicate that Klf5 plays a critical role in biliary epithelial tissue expansion and remodeling through induction of BEC proliferation, thereby contributing to liver regeneration.

やむを得ない理由の説明資料

８．博士論文の全部または一部が、単行本もしくは雑誌掲載等の形で刊行される予定である。

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「The transcription factor Klf5 is essential for intrahepatic biliary epithelial tissue remodeling against cholestatic liver injury 」