Roles of the primary bile acid receptor FXR in liver repair and tumorigenesis

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Abstract

Bile acids promote processing of dietary fat and regulate glucose homeostasis in liver through its receptor, FXR. In our study, we demonstrate that bile acid/FXR signaling also plays a role in the tissue homeostasis and repair as well as hepatocarcinogenesis. Either decreased bile acid level or loss of FXR leads to impaired liver regeneration after carbon tetrachloride-induced liver injury or 70% partial hepatectomy, which indicates that FXR is an essential liver protector by regulating liver cell proliferation and death. Indeed, FXR-/− mice spontaneously develop liver cancer when they are aged due to their chronic liver injury and deregulated repair. In addition, FXR expression is down-regulated in human liver tumors compared with non-tumor regions, and the hepatocarcinogenesis in FXR-/− mice can recapitulate the process of human liver cancer initiation and progression. Therefore, FXR-/− mice provide a unique animal model for liver cancer study. For instance, we generated IFNα-/−/FXR-/− mice to clarify the tumor suppressor role of the cytokine IFNα, the function of which was ever under debate. FXR-/− mice can be also used to identify or predict more differentially expressed genes in human liver cancer. For example, we found that one liver-rich miRNA, miR-194, which is down-regulated in the liver tumors of FXR-/− mice, is an important liver epithelial cell marker and prevents cancer metastasis, which has not been described before. In conclusion, ablation of FXR increases susceptibility to liver injury and tumorigenesis, and the FXR-/− mice provide a unique animal model for human liver cancer study.

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