Investigating the Protective Mechanisms of Fgf15 Against Hepatocellular Carcinoma (HCC) in Mdr2-KO Mouse Model: A Review of RNA-seq Analysis

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Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, and can develop in the setting of chronic liver inflammation and cirrhosis. Dysregulation of bile acids (BAs), as seen in conditions like cholestasis, is a contributor to inflammation-driven HCC. An important regulator of BA homeostasis in mice is the *Fgf15* gene that encodes Fibroblast growth factor 15 (FGF15). *Fgf15* regulates BA synthesis through negative feedback within the enterohepatic circulation system. FGF15 suppresses the synthesis of BAs, which could reduce cholestasis and therefore the severity of inflammation that drives HCC development. Using gene expression profiling, we sought to uncover key molecular mechanisms by which *Fgf15* overexpression protects against carcinogenesis in Mdr2-knockout (KO) mice, a model of cholestasis/inflammation-driven HCC. Livers were collected from male and female mice at 12-13 months of age, with and without the *Fgf15* transgene (four groups; n=3 per group). RNA sequencing (RNA-seq) was performed in each group to identify differentially expressed genes and examine enriched pathways. In male mice, *Fgf15* overexpression was associated with decreased expression of cell proliferation, inflammatory, and fibrotic genes, while potential tumor suppressor genes and metabolic regulators were upregulated. Interestingly, overexpression of *Fgf15* increased the expression of the female biased metabolic enzymes *Cyp2b9* and *Cyp2b13*, consistent with a previous study showing altered growth hormone signaling by *Fgf15* overexpression in male mice. These findings open new avenues of study for understanding *Fgf15* as a therapeutic target for cholestasis and liver injury and for identifying biomarkers. Supported by NIH R25ES020721.