Non-alcoholic steatohepatitis (NASH) is the most severe form of non-alcoholic fatty liver disease (NAFLD) and is a risk factor for hepatocellular carcinoma (HCC).

Accumulating evidence indicates that insulin resistance (IR) is associated with NASH and HCC carcinogenesis.

Hepatic lipid accumulation results from a combination of enhanced lipid delivery and uptake, increased de novo lipogenesis (DNL), and changes in fatty acid oxidation (FAO).

DNL is a risk factor linking NASH to HCC.

Our previous study demonstrates that fibroblast growth factor 21 (FGF21) inhibits the hepatocyte-Toll Like Receptor 4 (TLR4)-Interleukin 17A (IL-17A) signaling against NASH-HCC transition, but the effects of FGF21 on IR and DNL are unknown.

This study aims to investigate the role of FGF21 on hepatocyte IR and DNL.

Methods

Using the fourth-generation lentivirus packing system (Lenti-X, Takara-Clontech), FGF21 gene was knocked down (FGF21KD) in a mouse hepatocyte line, FL83B (ATCC CRL-2390), and a mouse hepatoma cell line, Hepa1-6 (ATCC CRL-1830).

Hepa1-6 and Hepa1-6 FGF21KD cells were grown in DMEM medium, while FL83B and FL83B-FGF21KD cells were grown in F12K medium. Cells were treated with 50 mM glucose and 25, 50, and 100 μM of sodium palmitate (FFA) as well as lipopolysaccharides (LPS), and insulin.

Oil Red O staining was performed to determine the lipid accumulation in the cells with treatments of FFA and IL-17A.

Western blot analysis was performed to detect protein expressions of phosphorylated hormone sensitive lipase (p-HSL) and IL-17A.

Total RNA was extracted from the cells and qPCR was performed to determine mRNA expression for fatty acid synthase (FASN) and acetyl CoA carboxylase (ACC1).

Results

Lack of FGF21 could promote hepatic steatosis and insulin resistance (IR) leading to de novo lipogenesis via upregulation of fatty acid synthase (FASN) and acetyl CoA carboxylase (ACC1), which might place an important role contributing to NASH-HCC transition.

Conclusion

Further studies are needed to investigate the accurate mechanism of FGF21 negative feedback on DNL contributing to lipid accumulation and IR during the NASH-HCC transition.

Future Direction

Acknowledgments

Funding by the R25-CA 134283 grant from the National Cancer Institute.