The Role of Intestinal Hepatocyte Nuclear Factor 4α in Alcoholic Liver Disease

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Abstract: Hepatocyte nuclear factor 4α (HNF4α) plays an important role in glucose and lipid metabolism. So far, the role of intestinal HNF4α in the pathogenesis of alcoholic liver disease (ALD) is unknown. In this project, we plan to use mice lacking intestinal HNF4α to investigate the role of HNF4α in ALD. The mice will be subjected to an NIAAA alcohol diet for 2 weeks. We will investigate whether loss of intestinal HNF4α protects against or aggravates ALD as well as the underlying mechanisms.

Background and rationale: ALD is one of the most common liver diseases worldwide. So far, the underlying mechanism is not well elucidated. HNF4α is expressed in the liver, pancreas, and intestine. Given that intestinal HNF4α regulates chylomicron secretion, intestinal HNF4α may also regulate alcohol absorption or metabolism.

Goals and objectives: We will investigate whether intestinal HNF4α plays a role in the pathogenesis of ALD and will also determine the underlying mechanism.

Investigative methods to be used: We will use the following mice: *Hnf4α*$^{fl/fl}$ mice and *Hnf4α*$^{fl/fl}$ X vilin-Cre (*Hnf4α*$^{INT-/-}$) mice. The mice will undergo the following protocol: mice will be fed a liquid control diet for 5 days, and then fed either a liquid control diet or a diet containing 5% alcohol for 10-15 days. On the last day of the study, the mice will be gavaged with alcohol and then euthanized after 9 h. Plasma and liver will be collected. Plasma levels of triglycerides (TG), cholesterol, AST, and ALT will be determined. Hepatic TG and cholesterol levels will also be determined. In addition, liver sections will be used for oil red O staining, H & E staining, and Sirius red staining (for staining of fibrosis). Hepatic mRNA levels of genes involved in lipid metabolism, inflammation, and fibrosis will be determined by qRT-PCR, and hepatic protein levels will be determined by Western blots. We predict that hepatic FOXA3 will protect against ALD.

Proposed method of data analysis: Student two-tailed t-test and one-way or two-way ANOVA (GraphPad Prism 10 software).

Significance of anticipated findings: The proposed studies will provide evidence regarding whether intestinal HNF4α plays a role in the development of ALD, and may lead to the identification of intestinal HNF4α as a novel target for treatment of ALD.

Mentoring Plan

Mentoring plan

The summer research student will be mentored by the lab's PI or a research scientist in the lab. The postdoctoral fellows and graduate students in the PI's lab will provide technical support for the student.

The PI will provide the summer research student with the background information and will work with the summer research student to develop the rationale, hypothesis, and approaches to test the hypothesis. The PI and his lab staff will work closely with the summer research student to make sure the project will move forward as expected.

The student will also attend the PI's weekly lab meeting and report the progress of the project in the lab meeting. The student will also present his/her data on the NEOMED's research/poster day.

Through this training, the student is expected to learn how to design studies to test a hypothesis. He/she will also learn lots of experimental techniques and how to work with animals, including animal gavage, RNA extraction, Western blots, Oil Red O staining, H & E staining, Sirius red staining, lipid extraction, measurements of AST, ALT, and lipids, etc.

Resources

All the mice and reagents are available for this study.

Performance site

NEOMED (PI's lab – F-205 and CMU for animal study).