

Fgf15 Overexpression and PPAR α Activation as a Combination Therapy for NASH in a Mouse Model

Author Block: M. F. Stofan, B. Kong, and G. Guo. *Rutgers, The State University of New Jersey, Piscataway, NJ.*

Non-alcoholic fatty liver disease (NAFLD) is a progressive disease that is increasing worldwide along with the obesity epidemic. Approximately 25% of the US population have NAFLD with up to 30% of that NAFLD population developing non-alcoholic steatohepatitis (NASH). Currently, there is no FDA approved treatment for NASH. One emerging therapeutic target for NASH is fibroblast-growth factor 19 (FGF19, mouse ortholog FGF15). This hormone is expressed in the small intestine and regulates bile acid synthesis and glucose homeostasis. Additionally, activation of peroxisome proliferator-activated receptor-alpha (PPAR α) increases fatty acid oxidation in hepatocytes and decreases triglycerides. Therefore, the overexpression of FGF15 in conjunction with a PPAR α agonist, was hypothesized to further reduce the severity of NASH in a mouse model. To investigate, 8 week old wild-type (WT; C57BL/6J) and transgenic *Fgf15* (*Fgf15*Tg) mice were maintained on a control diet (CD) or high-fat diet (HFD) for 6 months. PPAR α agonist WY-14643 (CAS #: 50892-23-4) (0.05% w:w) was administered for 6 weeks to HFD groups once NASH was induced at 4 months. HFD feeding increased body weight in both genotypes although *Fgf15*Tg mice were more resistant to weight gain. Glucose tolerance tests (GTTs) showed *Fgf15*Tg mice were more glucose tolerant, suggesting they are more insulin sensitive, while HFD decreased glucose tolerance in both genotypes. Serum levels of cholesterol and activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were decreased in *Fgf15*Tg mice after HFD feeding, suggesting hepatic protection. Activation of PPAR α promoted weight loss and decreased serum levels of cholesterol, triglycerides, ALT, and AST. In contrast, alkaline phosphatase (ALP) activity was increased after PPAR α activation. Combination treatment resulted in further weight loss, reduced serum levels of cholesterol, triglycerides, ALT, and AST; however, combination treatment did not further improve serum biochemical markers compared to individual treatments. *Funding:* R21ES029258, BX002741, T32ES007148.