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Steroid Hormones and Receptors

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Determining Mechanisms of Farnesoid×Receptor Regulation of Heme Biosynthesis and Ductular Reaction

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Bile acids are increasingly becoming recognized as hormones, and their main endogenous receptor is the farnesoid X receptor (FXR). In order to investigate whether FXR is necessary to maintain proliferation of the bile ducts in response to injury, we challenged male and female wild-type (WT) and Fxr knockout (FxrKO) mice with 0.1% 1,4 dihydro 2,4,6 trimethyl 3,5 pyridinediacarboxylic acid diethyl ester (DDC) in the diet for two weeks. DDC is an inhibitor of ferrochelatase, the final enzyme of heme biosynthesis, resulting in a buildup of bile plugs in the liver causing an inflammatory response called ductular reaction. We found that deletion of Fxr led to a dramatic reduction in the ductular reaction independent of the sex. Then we tested if the inhibition of ferrochelatase was compensated for in FxrKO mice by analyzing the expression of genes in the heme biosynthesis pathway. Although we find a decrease in basal Alad gene expression in FxrKO mice in both sexes, upon DDC treatment, expression does not decrease as much as seen in the WT mice. Intriguingly, we also noted sex-specific changes. Cpox expression was increased in male FxrKO mice, but FxrKO mice showed reduced suppression of Cpox expression when treated with DDC. Conversely, Ppox expression was reduced in male FxrKO mice compared to WT mice, and both male WT and FxrKO mice had a comparable reduction in Ppox expression upon DDC treatment. Female FxrKO mice showed a significant decrease in Fech expression basally that did not change with DDC treatment. These results suggest that FXR may contribute towards regulating expression of genes in the heme biosynthesis pathway. However, these observations do not explain the lack of ductular reaction. Since PGC1α was previously shown to control heme biosynthesis through its downstream targets, FOXO1 and NRF1, we examined their transcript expression in our study to determine if the pathway is playing a role in our observations. We examined this pathway and observed a significant decrease in Foxo1 expression in both sexes of WT and

FxrKO mice basally but only a reduction in Nrf1 expression upon DDC treatment. We are currently investigating other potential regulators of heme biosynthesis and ductular reaction, such as Klf1 which regulates erythropoiesis and plays a role in ductular reaction and the nuclear receptors Rev-Erbα/β that use heme as a ligand, to determine how FXR is regulating heme biosynthesis.

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