

The Role of FXR in Regulating the Hepatic Acute Phase Response in a Bacterial Model

Sammi Chung, Laura Armstrong, Bo Kong, Grace Guo

Fordham University and Rutgers, The State University of New Jersey

Farnesoid X receptor (FXR) is a ligand-activated nuclear receptor and a transcription factor, regulating bile acid synthesis and transport. FXR is highly expressed in the liver, and more recently FXR has been shown to play a key role in modulating inflammation. Studies have shown that FXR, when activated, acts as a protective agent against liver inflammation and potentially liver diseases such as nonalcoholic steatohepatitis, a part of fatty liver disease). Furthermore, FXR may regulate acute phase proteins, which are secreted as a result of acute phase response (APR)—a systemic reaction caused by infection, trauma, or tissue injury, and the APR is important for innate immunity. However, the exact mechanism is not well-established. Thus, the purpose of this study was to investigate the role of FXR in regulation of the hepatic APR using a bacterial infection model. To understand the mechanism and the effects, hepatocyte-specific FXR knockout mice (FXR^{hep} -/-) and wild-type control mice were injected with Escherichia coli (E. coli) intraperitoneally. Liver, spleen, and ileum were isolated 24 hrs following bacterial exposure, and in vivo bacterial counts in blood, liver, and spleen were determined. Gene expression of inflammatory cytokines (Tnf α , IL-1 β , IL-6,) and acute phase proteins (LCN2, LCN13, Mcp-1, and Saa3) were measured using quantitative PCR (qPCR) in both liver and spleen. While the results showed a diminished induction of acute phase proteins Mcp-1 and Saa3 and cytokines IL-1 β , IL-6, and Tnf α , FXR^{hep} -/- mice were not more susceptible to bacterial infection. There was an increase in serum ALT and AST levels in FXR^{hep} -/- mice, indicating that there was liver damage. In addition, the infection resulted in high levels of LCN2 for both the wild-type and FXR^{hep} -/- mice, whereas LCN13 expression was ablated in FXR^{hep} -/-, suggesting that FXR regulates LCN13 expression. To conclude, FXR may be a putative regulator of hepatic acute phase proteins.

