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Regulation of Bile Acid Homeostasis and Innate Immunity by Nuclear Receptors in the Intestine

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Bile acids play an essential role in the digestion and absorption of fats and lipophilic vitamins. However, bile acids are strong detergents that can damage enterohepatic tissues if their concentrations become too high. Bile acid concentrations are maintained at a safe level through the coordinate actions of nuclear receptors including the bile acid receptor, FXR, and the orphan nuclear receptors SHP and LRH-1. We are studying the function of these receptors in intestine, where they are all highly expressed. Evidence will be presented that activation of FXR in gut plays a crucial role in the regulation of bile acid homeostasis in liver and gallbladder. Among the genes induced by FXR in small intestine is fibroblast growth factor 15 (FGF15), which functions as a hormone. Mice lacking FGF15 have increased bile acid synthesis in liver and an empty gallbladder. Administration of FGF15 blocks bile acid production and causes rapid filling of the gallbladder. Activation of FXR in small intestine also induces genes involved in innate immunity. Mice lacking FXR have a marked increase in the number of intestinal bacteria and a compromised epithelial barrier function. Administration of a selective FXR agonist protects against bacterial proliferation and mucosal deterioration caused by biliary obstruction. Together, these data demonstrate that FXR in intestine plays a central role in enteroprotection and in the coordination of bile acid homeostasis in multiple tissues. Moreover, these data suggest that FXR agonists and FGF15 may be useful for treating a range of medical conditions associated with disruption of bile acid homeostasis including impaired bile flow.

Profile: After completing postdoctoral studies at the Salk Institute in La Jolla, California, in 1993, Dr. Kliewer joined Glaxo, Inc. in Research Triangle Park in North Carolina, where he co-founded a group to study orphan nuclear receptors as drug targets. In 2002, he moved to the University of Texas Southwestern Medical Center at Dallas where he is professor of molecular biology and pharmacology and holds the Hamon Distinguished Chair in Basic Cancer Research.