KLF15 Regulates Endobiotic and Xenobiotic Metabolism

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Hepatic metabolism and elimination of endobiotics (e.g., steroids, bile acids) and xenobiotics (e.g., drugs, toxins) is essential for health. While the enzymatic (termed phase I-II) and transport machinery (termed phase III) controlling endobiotic and xenobiotic metabolism (EXM) is known, our understanding of molecular nodal points that coordinate EXM function in physiology and disease remains incompletely understood. Here we show that the transcription factor Kruppel-like factor 15 (KLF15) regulates all three phases of the EXM system by direct and indirect pathways. Unbiased transcriptomic analyses coupled with validation studies in cells, human tissues, and animals, support direct transcriptional control of the EXM machinery by KLF15. Liver-specific deficiency of KLF15 (*Li-KO*) results in altered expression of numerous phase I-III targets, and renders animals resistant to the pathologic effect of bile acid and acetaminophen toxicity. Furthermore, *Li-KO* mice demonstrate enhanced degradation and elimination of endogenous steroid hormones, such as testosterone and glucocorticoid, resulting in reduced male fertility and blood glucose level, respectively. Viral reconstitution of hepatic KLF15 expression in *Li-KO* mice reverses these phenotypes. Our observations identify a previously unappreciated transcriptional pathway regulating metabolism and elimination of endobiotics and xenobiotics.