KLF15 Regulates Endobiotic and Xenobiotic Metabolism

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Abstract

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.

Image

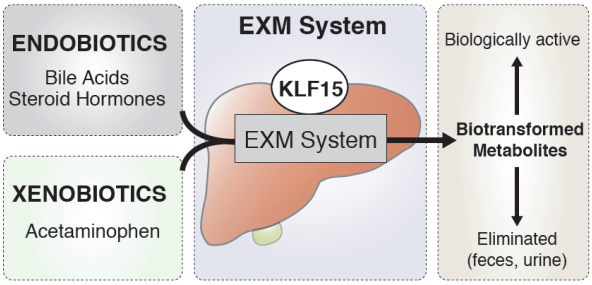


Figure 1. Schematic of KLF15-dependent regulation of EXM machinery and associated functions.

Recent Publications

1. Han S, et al. (2019) KLF15 regulates endobiotic and xenobiotic metabolism. Nature Metabolism 1:422-430.
2. Zhang R, Ray J, Jain M, Han S (2017) Ileectomy-induced bile overaccumulation in mouse intestine. The Journal of Visualized Experiments 126:e55728.
3. Han S, et al. (2015) Circadian control of bile acid synthesis by a KLF15-Fgf15 axis. Nature Communications 6:7231.
4. Han S, Cohen DE (2012) Functional characterization of Thioesterase superfamily member 1/acyl-CoA thioesterase 11: implication for metabolic regulation. Journal of Lipid Research 53:2620-2631.
5. Jeyaraj D, et al. (2012) KLF15 orchestrates circadian nitrogen homeostasis. Cell Metabolism 15:311-323.

Photograph



Dr. Shuxin Han has been engaged in metabolic biology research for nearly 15 years. Dr. Han mainly studies the transcriptional regulation of metabolism by various transcription factors from previously nuclear receptors to currently kruppel-like factor (KLF) family. His recent academic achievements include three parts. First, Dr. Han opens a new research area of the KLF family regulation of endobiotic and xenobiotic metabolism. Second, Dr. Han discovers a novel patent therapeutic target for several human diseases such as liver injury and infertility. Third, Dr. Han expands and deepens the field of surgery metabolism.

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Notes/Comments: