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Abstract

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.

Biography:

Shuxin Han has dedicated to metabolic biology for 15 years, mainly studying the transcriptional regulation of broad endogenous and exogenous compound metabolism by transcription factors (e.g., Kruppel-like factor/KLF, nuclear receptors). He

has published articles in the high-level journals like Molecular Endocrinology, PNAS, Nature Communications, and Nature Metabolism. Dr. Han is now serving as a faculty member at University of Science and Technology of China First Affiliated Hospital and as the head of Central Nodal Bioscience and Technology Research Center and in Hefei, Anhui Province, China.

Recent Publications:

1. Shuxin Han, et. al., Mukesh Jain, 2019. KLF15 regulates endobiotic and xenobiotic metabolism. Nature Metabolism, 1; 422-430
2. Shuxin Han, et. al., Mukesh Jain, 2015. Circadian control of bile acid synthesis by a KLF15-Fgf15 axis. Nature Communications, 6: 7231
3. Shuxin Han, et. al., John Chiang, 2010. A novel bile acid-activated vitamin D receptor signalling in human hepatocytes. Molecular Endocrinology, 24: 1151-1164

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