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Transcriptional Regulation of Bile Acid Metabolism and Microsurgery

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Circadian control of nutrient availability is critical to efficiently meet the energetic demands of an organism. Production of bile acids (BA), which facilitate digestion and absorption of nutrients, is a major regulator of this process. Here we identify a KLF15-Fgf15 signaling axis that regulates circadian BA production. Systemic Klf15 deficiency disrupted circadian expression of key BA synthetic enzymes, tissue BA levels and triglyceride/cholesterol absorption. Studies in liverspecific Klf15-knockout mice suggested a non-hepatic basis for regulation of BA production. Ileal Fgf15 is a potent inhibitor of BA synthesis. Using a combination of biochemical, molecular and functional assays (including ileectomy and bile duct catheterization), we identify KLF15 as the first endogenous negative regulator of circadian Fgf15 expression. Elucidation of this novel pathway controlling circadian BA production has important implications for physiologic control of nutrient availability and metabolic homeostasis. Surgery model like intestinal resection is a common therapeutic approach for human diseases such as obesity, inflammatory bowel disease, Crohn's disease, and colon cancer that often results in severe short bowel syndrome-like adverse effects including bile acid diarrhea, dehydration, electrolyte disturbances, and nutrient malabsorption. We introduce a murine ileal resection model, termed ileectomy, to evaluate tissue communication and the maintenance of systemic homeostasis. Bile is the important cycling fluid in our body composed of multiple components critical for many functions. Here, we successfully established a murine bile duct catheterization (MBDC) model to collect the pure bile continuously from mice under the conscious status. These two novel microsurgery models may provide invaluable platforms for various physio-pathological studies such as ileal regulation of systemic metabolism and diseases, lipid and drug metabolism as well as the diagnosis and prognosis of human diseases like pancreatic and biliary tract cancers.

Biography

I am currently a Senior Research Associate at Case Western Reserve University in Cleveland, Ohio in the US. I will join as a faculty member at the School of Animal Science at Anhui Agricultural University in Hefei, Anhui in China this October. I have been engaged in the metabolic biology for thirteen years. The studies broadly cover the metabolism of endogenous metabolites (e.g., bile acids, steroids, fat, ketone body, and glucose) to exogenous compounds (e.g., drugs). The studies have been mostly focusing on the transcriptional regulation of metabolism by various transcription factors from previously nuclear receptors to currently developmental transcription factors. In the past years, I have been dedicating to the study of developmental transcription factor Kruppel-like factor (KLF) family and developed the novel critical fields of transcriptional regulation of endo- and xenobiotic metabolism under physiological and chemical or surgery induced disease conditions.

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