Regulation of Liver Energy Balance by Nutrient-sensing Nuclear Receptors

Kangho Kim[1], Geoffery A. Preidis[2] and David D. Moore[1]

Departments of [1]Molecular and Cellular Biology and [2]Pediatrics, Baylor College of Medicine, Houston, TX 77030
moore@bcm.edu

The nuclear receptors PPARα (encoded by NR1C1) and farnesoid X receptor (FXR, encoded by NR1H4) are activated in the liver in the fasted and fed state, respectively. PPARα activation induces fatty acid oxidation, while FXR controls bile acid homeostasis, but both nuclear receptors also function coordinately to control other metabolic pathways relevant to liver energy balance, including fatty acid oxidation and gluconeogenesis in the fasted state and lipogenesis and glycolysis in the fed state. These receptors have mutually antagonistic impacts on another pathway very relevant to energy balance, autophagy, which is induced by PPARα but suppressed by FXR. A less obvious, but very important pathway for energy balance is the hepatic secretome, which is a major drain on liver energy and nutrient resources. We have found that the liver secretome is directly suppressed by PPARα, but induced by FXR. This discovery is linked to human development by previous studies demonstrated a striking deficiency in bile acid levels in malnourished mice and also in malnourished children. Further results confirm that the fasting activated PPARα is activated in undernourished mouse models. We have found that multiple hepatic targets of PPARα and FXR are dysregulated in chronic undernutrition. This includes repression of liver secretome components in the complement and coagulation cascades, and undernourished mice show blood coagulation defects that are also observed in malnourished human subjects. We conclude that PPARα and FXR function coordinately to integrate liver energy balance.