J Liver 2016, 5:2(Suppl)
http://dx.doi.org/10.4172/2167-0889.C1.006

Hippo signaling in liver development, homeostasis, and disease

Randy L Johnson
University of Texas MD Anderson Cancer Center, USA

Hippo signaling is an evolutionarily conserved growth and organ size control pathway that has essential roles in embryogenesis, adult tissue homeostasis, and is frequently aberrantly regulated in pathological situations such as cancer. Our laboratory has been studying the role of Hippo signaling in regulating liver development, homeostasis, and disease. By using a combination of mouse models, *in vitro* differentiation assays and comparative genomics we have shown that Hippo signaling regulates liver progenitor cell differentiation during late gestation and early postnatal life, functions to maintain hepatocyte quiescence in the mature liver is a potent tumor suppressor pathway in mice and is frequently deregulated in human hepatocellular carcinoma. Currently we are focusing on identification of genes and pathways that cooperate with Hippo signaling to maintain homeostasis in the adult liver and to prevent malignant transformation. To that end we have carried out an *in vivo* mutagenesis screen and identified 81 candidate genes that work together with Hippo signaling to repress tumor formation and/or tumor progression in a mouse model for liver cancer. The design and results of our screen and analysis of interaction of Hippo signaling with selected genes will be discussed. Overall, our results highlight the Hippo signaling pathway as an essential modulator of liver development, homeostasis and disease.

rljohnso@mdanderson.org

Bile acid signaling activates MiR-26a to regulate insulin sensitivity and metabolism of glucose and lipids

Wendong Huang
City of Hope Diabetes and Metabolism Research Institute, USA

Type 2 diabetes (T2D) is characterized by insulin resistance and increased hepatic glucose production, yet the molecular mechanisms underlying these abnormalities are poorly understood. GPBAR1/TGR5 is a G protein–coupled receptor of bile acids. TGR5 is known to regulate the BA homeostasis and energy metabolism. Recent studies highlight an important role of TGR5 in alleviating obesity and improving glucose regulation, however, the mechanism of which is still unclear. Here we report that TGR5 is involved in mediating the anti-obesity and anti-hyperglycemia effect of a natural compound, oleanolic acid. By comparing the miRNA profiles between wild type and $TGR5^{-/-}$ livers after OA treatment, we identified miR-26a as a novel downstream target gene of TGR5 activation. MicroRNAs (miRNAs) are a class of small non-coding RNAs that play important roles in human diseases, including T2D. MiR-26a plays critical roles in tumorigenesis, however its function in cellular metabolism remains unknown. Here we identify miR-26a as a novel regulator for insulin signaling and metabolism of glucose and lipids. Expression of miR-26a in the liver is decreased in two obese mouse models and in overweight humans. Global or liver-specific overexpression of miR-26a in mice improves insulin sensitivity, decreases hepatic glucose production, and decreases fatty acid synthesis, thereby preventing obesity-induced metabolic complications. Conversely, silencing of endogenous miR-26a in mice impairs insulin sensitivity, enhances glucose production, and increases fatty acid synthesis. Mechanistically, miR-26a targets several key regulators of hepatic metabolism and insulin signaling. These findings reveal a novel role of miR-26a in regulating liver metabolism, and provide a potential target for the treatment of T2D.

whuang@coh.org