Tick-Tock Hedgehog-Mutual crosstalk with liver circadian clock promotes liver steatosis.

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Abstract

Background & Aims: The mammalian circadian clock controls various aspects of liver metabolism and integrates nutritional signals. Recently, we described Hedgehog (Hh) signaling as a novel regulator of liver lipid metabolism. Here, we investigated crosstalk between hepatic Hh signaling and circadian rhythm.

Methods: Diurnal rhythms of Hh signaling were investigated in liver and hepatocytes from mice

with ablation of Smoothened (SAC-KO) and crossbreeds with PER2::LUC reporter mice. By

using genome-wide screening, qPCR, immunostaining, ELISA and RNAi experiments in vitro we identified relevant transcriptional regulatory steps. Shotgun lipidomics and metabolic cages were used for analysis of metabolic alterations and behavior.

Results: Hh signaling showed diurnal oscillations in liver and hepatocytes in vitro. Correspondingly, the level of Indian Hh, oscillated in serum. Depletion of the clock gene Bmal1 in hepatocytes resulted in significant alterations in the expression of Hh genes. Conversely, SAC-KO mice showed altered expression of clock genes, confirmed by RNAi against Gli1 and Gli3. Genome-wide screening revealed that SAC-KO hepatocytes showed time-dependent alterations in various genes, particularly those associated with lipid metabolism. The clock/hedgehog module further plays a role in rhythmicity of steatosis, and in the response of the liver to a high fat diet or to differently timed starvation.

Conclusions: For the first time, Hh signaling in hepatocytes was found to be time-of-day dependent and to feed back on the circadian clock. Our findings suggest an integrative role of Hh signaling, mediated mainly by GLI factors, in maintaining hepatic lipid metabolism homeostasis by balancing the circadian clock.

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