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Circadian rhythms govern liver biology in health and disease

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Statement of the Problem: The liver is a primary organ controlled by the circadian clock. Circadian transcripts in the liver are involved in highly organ-specific functions, including glucose homeostasis, lipogenesis, bile acid synthesis, mitochondrial biogenesis, oxidative metabolism, amino acid turnover, and xenobiotic detoxification. Environmental or genetic disruption of the circadian clock exacerbates predisposition to non-alcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma (HCC). However, the molecular mechanisms underlying the clock surveillance of liver biology and disease pathogenesis remain enigmatic.

Methodology & Theoretical Orientation: Our series of studies applied tools of genetics, epigenetics, and animal disease models aiming to dissect the roles of the circadian clock in liver physiology. Findings: The lineage-specifying nuclear receptor HNF4A establishes liver-specific circadian rhythms by means of creating permissive chromatin structure for occupancy of circadian clock transcription factors at target genes. We also found that the central clock components BMAL1 and CLOCK promote HCC tumor growth by controlling cell cycle regulators WEE1 and p21.

Conclusion & Significance: First, our results provide a molecular basis for circadian gene expression in the liver which governs daily oscillation of most principle hepatic physiological processes. Second, our results provide molecular insights into the HCC-clock crosstalk by unveiling that the core clock components are hijacked by cancer cells to fuel rapid cell proliferation and inhibit apoptosis. Therapeutics targeting the molecular clock have thus strong potential to be explored either as a immunotherapy or in combination with current first-line therapies in treatment of HCC.

Biography

Dr. Meng Qu has her expertise in the studies of circadian clock regulation of human diseases. She has uncovered the molecular mechanisms of clock-controlled liver functions in both health and disease states. Dr. Qu aims to apply tools including high-throughput multi-omics to decipher the reciprocal regulation between circadian rhythms and carcinogenesis in the liver and gastrointestinal track. She is also investigating efficacy of clock-targeting compounds in treating cancers within animal models. These studies may lay a foundation for the discovery of novel therapeutic strategies. Dr. Meng Qu recently joined Zhejiang University as an assistant professor..