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Circadian Disruption of the CLOCK-BMAL1 Axis in Hepatic Stellate Cells Promotes Fibrosis Progression in Non-Alcoholic Steatohepatitis

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Abstract

Non-alcoholic steatohepatitis (NASH) progression exhibits diurnal patterns, yet the molecular clock's role in hepatic fibrogenesis is unknown. We demonstrate that hepatic stellate cells (HSCs) possess autonomous circadian clocks that regulate collagen synthesis and autophagy. Disruption of *Clock* or *Bmal1* in HSCs through genetic knockout or environmental circadian disruption (chronic jet-lag) accelerated fibrosis in methionine-choline deficient (MCD) diet-fed mice. Mechanistically, CLOCK-BMAL1 directly bound the *Col1a1* promoter and repressed TGF-β signaling through period protein interactions. Chronotherapeutic administration of losartan during the active phase maximized HSC quiescence restoration. Targeting circadian pathways offers a temporal therapeutic strategy for NASH fibrosis.

Keywords: circadian rhythm, hepatic stellate cells, NASH, CLOCK-BMAL1, liver fibrosis, chronotherapy