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Effect of Feeding Regimens of YAP Signaling

College of Sciences and Health Professions

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Abstract

Many mammalian physiological and behavioral aspects show 24-hour circadian rhythms such as metabolism, sleep-wake cycle, body temperature and blood pressure. These 24 hour rhythms are regulated by circadian clocks, which are internal timekeeping systems located in every body cell and tissue, and synchronize these rhythms with the external environment. At the molecular level, CLOCK and BMAL1 are core clock genes involved in transcription-translation feedback loop which in turn regulate biological processes and coordinate them with daily rhythms. Circadian clock has been demonstrated to regulate cell cycle, cell proliferation and differentiation, but the mechanism in liver is not clearly known. Hippo pathway is an evolutionarily conserved pathway that plays an important role in regulating organ size, cell growth and cell differentiation. Hippo acts as a negative regulator of YAP1 by inducing phosphorylation and sequestration in the cytoplasm, thereby inactivating YAP1; on the other hand, switching off Hippo activates YAP1, thus enabling the translocation to the nucleus and promoting the transcription of pro-proliferative genes. How Hippo signaling and circadian clocks interact is not known. It is also established in multiple studies that peripheral clocks such as in liver are regulated by feeding cues; how these cues affect Hippo signaling in liver is also not known. Hence we plan to investigate the interaction of feeding cues and circadian clock with Hippo signaling. We applied two different feeding paradigms and analyzed transcriptional and translational activity of YAP1. Our initial observations suggest that feeding regimens have differential effect on YAP1 phosphorylation and YAP1 downstream targets. We further investigated this interaction at the transcriptional level in clock mutant mice (*Bmal1* and *Cry1,2^{-/-}*) using two of well-known targets of YAP1, *Ctgf* and *Cyr61*. While circadian control of *Ctgf* is CR dependent, on the other hand, *Cyr61* rhythmicity is regulated in a time dependent manner and is independent of circadian control and feeding paradigms, thus above results suggest a complex interaction between Hippo, clocks and feeding cues.