

Uncovering the link between the Hippo pathway and circadian clock.

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The circadian clock is a cell intrinsic timekeeping system that regulates daily variation in several biochemical and physiological processes, including cell growth, metabolism and tissue repair. At the molecular level, circadian clocks are based upon interconnected transcription-translation feedback loops in which the transcriptional activators CLOCK and BMAL1 heterodimers binds the promoters region of clock and clock controlled genes such as PERIOD (PER1/2) and CRYPTOCHROME (CRY1/2). PER and CRY proteins in turn feedback to inactivate CLOCK and BMAL1 heterodimers.

This feedback loop controls transcriptional activity and daily variation in transcripts levels of several thousands of genes in various organs. Recent reports suggest a possible link between the Hippo pathway and the circadian clock. For example, YAP mediated NF- κ B activation alters clock gene expression in sarcoma. It was further reported that the circadian clock in intestinal stem cells is positively regulated by the Hippo pathway. However, whether these effects are directly under the control of the Hippo pathway components or their effector proteins is unclear.

In the present work, we deepen this knowledge by showing that YAP is a direct regulator of Cry1 transcription. Indeed, YAP binds to the proximal promoter region of Cry1 and positively regulates its transcription in TEAD dependent manner. Interestingly, we have shown that Cry1 acts in a feedback loop to modulate YAP/TAZ transcription and Hippo pathway activity.