HIGHLIGHTS

GENE EXPRESSION

Circadian clock and cell division: unveiling the link

Daily oscillations in many biological processes, all of which are controlled through an endogenous circadian clock, occur during a 24-hour period. This clock measures changes in light and mediates photoperiodic responses. Previous research indicated that circadian rhythms could control the activity of the cell cycle, but only now has work by Hitoshi Okamura and colleagues shown that the underlying mechanism involves direct transcriptional regulation of the cell-cycle gene *Wee1* by Clock — a master control switch of circadian gene expression.

Using a mouse model with a partial hepatectomy (PH), Okamura and colleagues analysed the relationship between the circadian clock and the cell cycle. Liver cells from wild-type mice that have undergone a PH rapidly re-enter the cell cycle and restore the liver in a few days. The rate of liver regrowth was studied in mice that were maintained in a 12-hour light/dark cycle, with a PH on the liver performed at the start of the 12-hour light period (ZT0) and 8 hours later (ZT8). The results of BrdU incorporation, which marks cell proliferation, indicated that although S-phase kinetics were similar for both ZT0 and ZT8, there was a delay in cells entering mitosis if the PH was performed at ZT0. This shows that the timing of the hepatectomy affects cell-cycle progression in the regenerating cells. Peaks of the cell-cycle kinase Cdc2 and mRNA levels of other cell-cycle regulators, including *Wee1* — which is a known Cdc2 regulator — mimicked the BrdU incorporation peaks and pointed to the involvement of cell-cycle regulators in this process.

Performing a PH on mice that are mutant for known clock regulators, such as the blue-light sensitive photoreceptor cryptochromes (*cry*), prevented normal liver regeneration and inhibited the peak of Cdc2 activity. Levels of Wee1 were increased in *cry*-mutant mice, but decreased in *clock*-mutant mice. Clock regulates gene expression by binding E-box motifs and three of these were identified in the 5′ UTR of *Wee1*. When these regions are mutated, transcription of *Wee1* by Clock/Bmal1 is decreased, presumably because Clock no longer binds upstream of *Wee1* to regulate its transcription. This indicates a direct but unidirectional regulatory mechanism (the authors show that there is no feedback) between the circadian clock and cell-cycle regulation.

As the molecular mechanisms that underlie the action of the circadian clock are still poorly understood, further genetic analysis of the links between cell-cycle regulators and clock components should provide important clues as to this control mechanism.

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References and links

ORIGINAL RESEARCH PAPER Matsuo, T. *et al.* Control mechanism of the circadian clock for timing of cell division *in vivo*. *Science* 23 August 2003 (10.1126/science.1086271)

FURTHER READING Panda, S. *et al.* Circadian rhythms from flies to humans. *Nature* **417**, 329–335 (2002)