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Orphan nuclear receptors, molecular clockwork, and the entrainment of peripheral oscillators.

[Preitner N](#), [Brown S](#), [Ripperger J](#), [Le-Minh N](#), [Damiola F](#), [Schibler U](#).

Department of **Molecular** Biology, NCCR Frontiers of Genetics, Sciences II, University of Geneva, 30, Quai Ernest Ansermet, CH-1211 Geneva, Switzerland.

Abstract

Here we summarize our work on two aspects of circadian timing: the roles of **orphan nuclear receptors** in the **molecular clockwork**, and phase **entrainment** of **peripheral oscillators**. With reference to the former, studies on cis-acting regulatory elements within the Bmal1 promoter revealed that REV-ERBalpha, an **orphan nuclear** receptor provides a link between the positive and negative limbs of the **molecular** oscillator. Specifically, REV-ERBalpha controls the cyclic transcription of Bmal1 and Clock, the positive limb components. In turn, the circadian expression of Rev-Erbalpha itself is driven directly by the **molecular** oscillator: it is activated by BMAL1 and CLOCK, and repressed by PERIOD1/2 and CRYPTOCHROME1/2 proteins (the negative limb members). With regard to phase **entrainment**, it was initially believed that only the suprachiasmatic nucleus (SCN) was capable of generating circadian rhythms. However, circadian **oscillators** have recently been discovered in many **peripheral** tissues. In the absence of a functional SCN pacemaker, these **peripheral** clocks dampen after a few days. Hence, the SCN must periodically synchronize these subsidiary timekeepers. It may accomplish this task mostly through an indirect route: namely, by setting the time of feeding. In addition to feeding cycles, body temperature rhythms and cyclically secreted hormones might also serve as zeitgebers for **peripheral** clocks.

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