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Frank Weber

Circadian Regulation and Biological Timing

Goal

To understand the molecular and neuronal program that facilitates a temporal synchronization of physiology and behaviour by the circadian clock. Specific aims:

1. **How transcription factor activity can be precisely controlled to specific times.**
2. **How cellular and circadian signalling cross-talk in order to temporally coordinate genome-wide transcription and physiology.**
3. **How neuronal and cellular signalling networks control behaviour.**

Background

Most organisms regulate their physiological, metabolic, and behavioural activities in a rhythmic fashion and in synchrony with the environmental cycles of day and night. Circadian rhythms are controlled by a set of transcription factors that assemble a molecular circadian clock, which is able to maintain a self-sustained 24-hour oscillation. Circadian regulation provides a vital advantage by allowing a temporal separation and coordination of homeostatic functions, such as an up-regulation of apoptotic and DNA-repair genes prior to sunrise or of metabolic enzymes prior to food uptake. Malfunction of the circadian system is associated with diseases, such as sleeping-, bipolar-, and depressive-disorder, diabetes, Alzheimer disease and increased tumorigenesis.

We investigate the assembly and regulation of the circadian clock in the model organism *Drosophila*, which is homologous to the clock in mammals. Our goal is to understand how physiology and behaviour are temporally orchestrated, and we aim to gain insights into general mechanisms of biological timing that are similarly important for accurate cell cycle and developmental regulation.

Research Highlights

1) The timing of transcription factors

The core oscillating activity of the circadian clock in *Drosophila* and mammals is formed by the heterodimeric complex of transcription factors CLOCK (CLK) and CYCLE (CYC). Particularly rhythmic regulation of CLK is crucial for circadian clock function. We showed that a sequential and

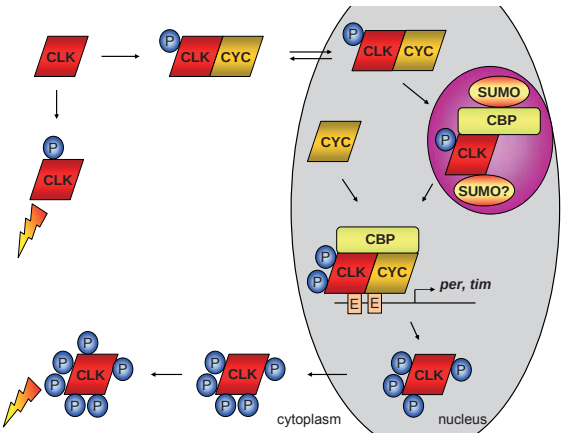

Fig.1: *A post-translational interval-timer of the Drosophila circadian clock based on sequential and compartment-specific modification of the CLK protein.*

compartment-specific phosphorylation controls the life cycle of the CLK protein, uncovering a post-translational timing mechanisms of the circadian clock. Our results indicate that every step of the CLK life cycle is precisely controlled by co-factor and DNA interactions, as well as by a cascade of specific post-translational modifications that include phosphorylation, SUMOylation and ubiquitination. The sequence of specific interactions and modifications allows a precise timing of CLK accumulation, nucleo-cytoplasmic transport, localization to PML-like nuclear bodies, transcriptional activation, inhibition, and finally degradation (Fig. 1). We were able to identify specific phosphorylation sites and kinases that control individual steps in the life cycle of the CLK protein. Unravelling the regulation of the CLK protein provides important insights into molecular mechanisms that allow a precise temporal control of transcription factors in general and of circadian transcription in particular.

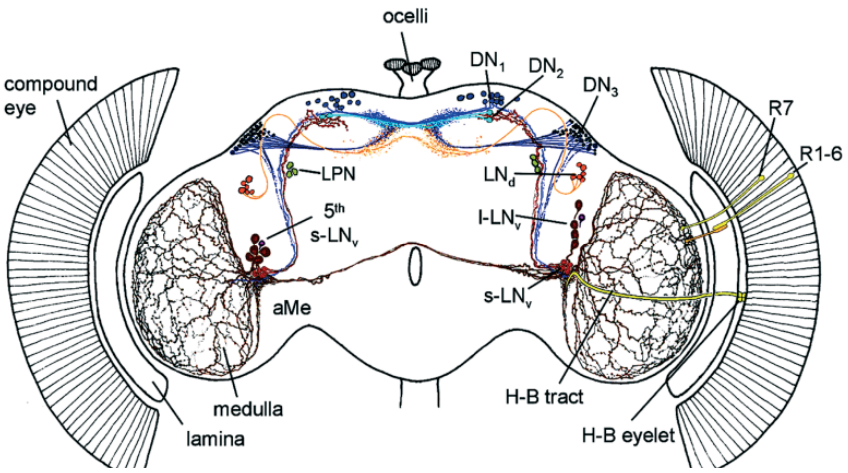

Fig. 2: *Distinct sets of neurons assemble a network that controls circadian behaviour (figure adopted from Helfrich-Förster C et. al. J Comp Neurol. (2007) 500:47-70.).*

2) Temporal regulation of physiology

We investigate the cross-talk between circadian and cellular signalling pathways to better understand the signalling network that allows a rhythmic organisation of homeostatic functions such as metabolism, cell proliferation, and neuronal activity. We found that cyclic-nucleotide/PKA, calcium/CaMKII and Ras/MAPK pathways contribute to the regulation of circadian transcription, partially by direct phosphorylation of the CLK protein and partially through regulation of the CREB-binding protein (CBP), which we showed to act as a co-activator and regulatory factor of CLK/CYC-dependent transcription. These signalling pathways are likely involved in the regulation of circadian transcription by metabolic and behavioural activity.

3) Neurobiology of circadian behaviour

In order to gain insights into neuronal network structures that underlay circadian behaviour we investigate the siesta-phenotype in flies. At low temperature flies like humans are highly active during midday, while at high temperature behavioural activity is shifted to morning and evening hours with a pronounced 'siesta' during midday. Morning and evening behavioural activity are controlled by distinct groups of neurons (Fig. 2). We investigated neuropeptide signalling between circadian neurons, which we found to contribute to the regulation of siesta time. In addition, we showed that the chaperone HSP90 is important for fine tuning variability and stability of circadian behavioural phenotypes, which is particularly interesting with regard to the evolution of new behavioural traits.

Selected Publications

H-C. Hung, C. Maurer, D. Zorn, W-L. Chang and F. Weber (2009) Sequential and compartment-specific phosphorylation controls the life cycle of the circadian CLOCK protein. *J. Biol. Chem.* 284:23734-23742.

C. Maurer, H-C. Hung and F. Weber (2009) Cytoplasmic interaction with CYCLE promotes the post-translational processing of the circadian CLOCK protein. *FEBS letters* 583:1561-1566.

H-C. Hung, S. Kay and F. Weber (2009) HSP90, a capacitor of behavioural variation. *J. Biol. Rhythms*. 24:183-192.

R. Brunsing, S.A. Omori, F. Weber, A. Bicknell, L. Friend, R. Rickert, M. Niwa (2008) B- and T-cell development both involve activity of the unfolded protein response pathway. *J. Biol. Chem.* 283:17954-17961.

H-C. Hung, C. Maurer, S.A. Kay and F. Weber (2007) Circadian transcription depends on limiting amounts of the transcription co-activator nejire/CBP. *J. Biol. Chem*. 282:31349-31357.

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