Interactions of the F Box Protein Jetlag in Circadian Clocks

Jerdon Dresel, Kate Scheuer, and Laurence Loewe

Laboratory of Genetics and Wisconsin Institute for Discovery, University of Wisconsin-Madison

What are circadian clocks?

Circadian clocks are a key biological function that controls our internal timekeeping in day to day life[5]. Without these clocks the human body would not be able to adapt correctly to a new environment after prolonged east-west travel or be able to regulate daily functions. While much is known about the genetic functionality of these clocks, there are still important questions that remain unclear. One example is how the Jetlag (JET) F box protein interacts with the photoreceptor Cryptochrome (CRY) to degrade a central clock protein, Timeless (TIM), in our model organism *Drosophila melanogaster*. TIM is thought to control daily resetting of circadian clocks in a light-dependent environment via conformational changes in CRY. This degradation is thought to be the main contributor to phase shifts in the circadian clock and failure to regulate it properly may lead to irregular sleep patterns and so called "jetlag."

Why study JET?

The entire JET-TIM degradation pathway comprises only a small portion of the entire circadian clock model. Why then is JET so important to the clock as a whole? Simply put, JET acts as the enabler for the "reset" button, which is realized by TIM degradation in the circadian clock cycle alongside a sister F-box protein known as Slimb (SLMB)[2]. Under dark environmental conditions SLMB maintains TIM degradation in stead of JET as CRY cannot initiate the JET-TIM degradation pathway without blue light radiation from the environment. Together, JET and SLMB allow for an organism to adjust to new environments and maintain rhythmicity with a light-dark cycle[2] . Rapid travel in either an East or West direction causes this fine balance in light-dark cycles to become unbalanced by experiencing too much or too little of a light stimulus. The resulting effect is an arrhythmic pattern in circadian clocks which causes the symptoms that gave JET its name, 'jetlag'. Knowing this degradation pattern and the circadian clock as a whole may help to alleviate a few of these symptoms.

Cryptochrome:

Cryptochrome is a crucial component of the JET-TIM degradation pathway as the entire process is dependent on the initial response of CRY to blue light radiation. As TIM is not a photoreceptor itself, it requires the help of CRY to undergo degradation in a lighted environment. During this first stage, CRY undergoes a conformational change at its C-terminal when struck with such radiation[4]. This structural change converts CRY from an "inactive" state to an "active" one that is able to interact with TIM and allows for downfield genetic components to further affect TIM degradation. During this process CRY is also attacked by JET for degradation. However, the affinity of JET to TIM is much higher than to CRY, thus, CRY is degraded at a slower rate than TIM.

COP9 Signalosome:

During the interactions of JET, the COP9 signalosome (CSN) is required for the efficient degradation of TIM within the circadian clock[2]. CSN acts upon TIM degradation by removing Nedd8, an ubiquitin-like modifier, from the SCF complex that is composed with the F-box protein JET. This action allows for the crucial final step in JET-TIM degradation by initiating chemical compatibility between the two.

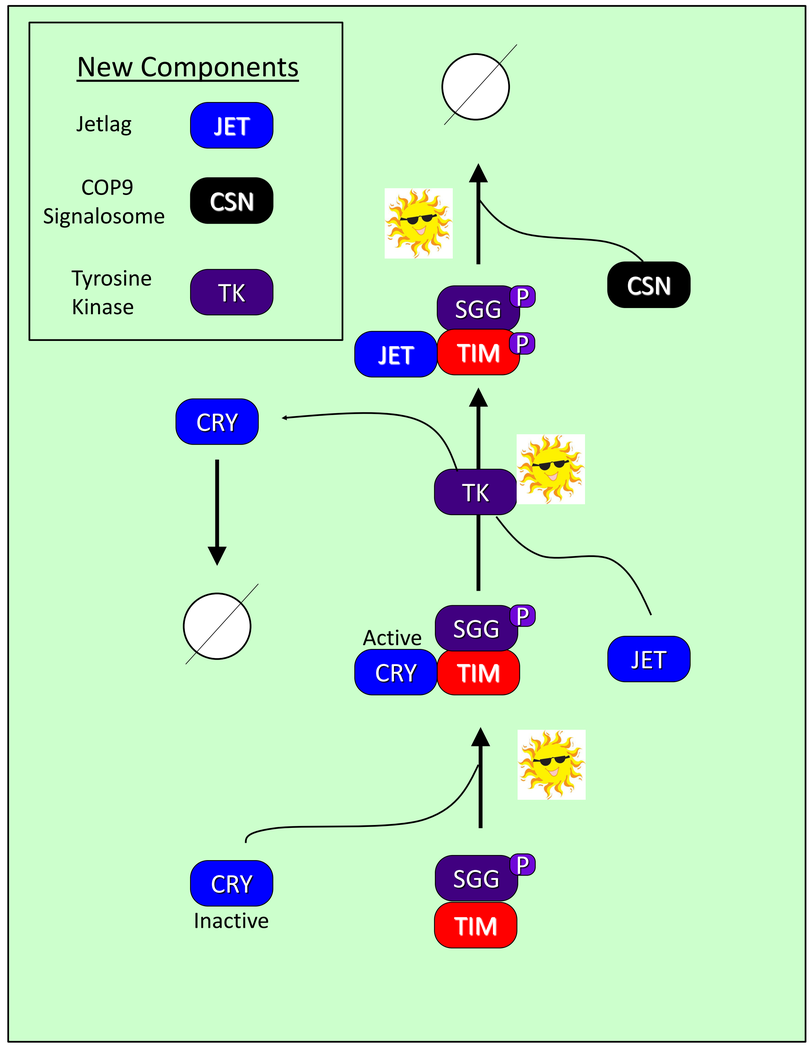

Figure 1: A new proposal on the intricate JET-TIM degradation pathway based on the most current model

Jetlag:

The F box protein JET is the central factor in light-dependent TIM degradation. JET does this through being part of the Skp1/Cullin/F-Box E3 ubiquitin ligase complex that has the responsibility of the ubiquitination and degradation of TIM[2]. It acts through this complex as a gateway for light signals between CRY and TIM[3]. By acting as the middle man between these two genetic components it connects both ends of TIM degradation that allows for the entire process to work as a coordinated system.

An Unknown Component

A vital yet mysterious factor that comes into play during JET-TIM degradation pathway is an unknown tyrosine kinase that is responsible for the phosphorylation of TIM[1]. This phosphorylation is a form of post –translational modification that is required for TIM to be structurally compatible with JET to begin the process of degradation. Further investigation is needed to fully understand this vital component and its true identity.

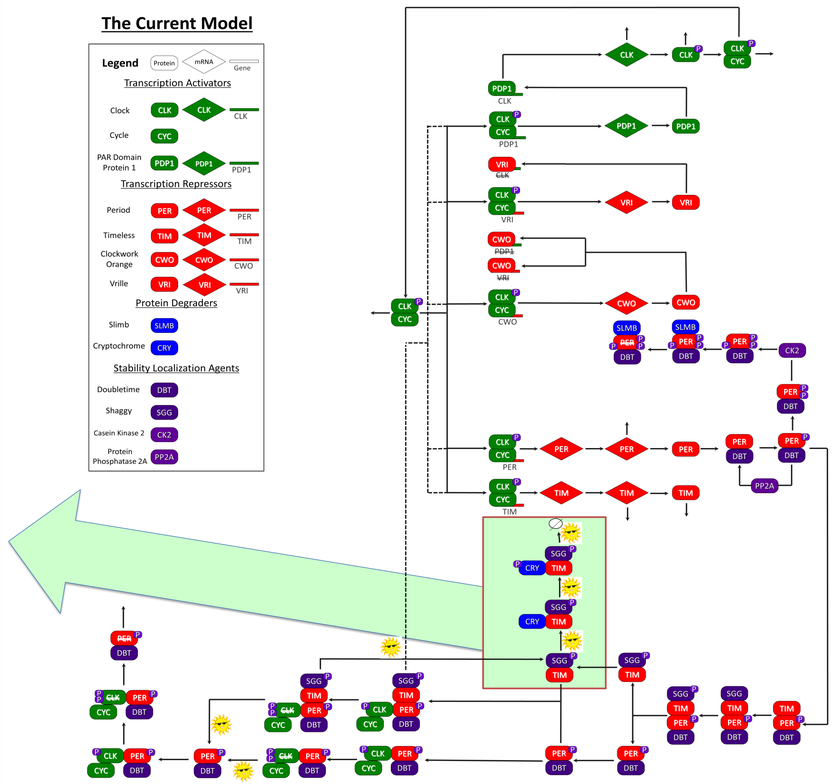

Figure 2: The current model produced by Kate Scheuer of the pathways of the circadian clock in *Drosophila melanogaster*

Proposing a Model for Oscillations

Circadian clocks must be very reliable oscillators, since they have been in operation for millions of years, supporting the ability of organisms to adapt seasonal changes and other fluctuations. Using the interactions we investigated, we hope to construct a fully functional computer generated model that can be simulated to produce time courses. This model should help us to estimate credible values for the parameters of the reactions identified during our research. A generated model will also confirm less understood mechanisms of the circadian clock such as when and in what amounts JET enters the system. This will help us to better understand the daily oscillations of TIM and the ability to adapt to separate time zones as well as new environments. Experiments showed that during rhythmic cycling of TIM in the circadian clock, TIM's concentration fell sharply early in the day and only started to accumulate during the early portions of the night[5]. Hopefully, our models of this daily rise and fall will be able to help us understand the causal mechanisms better and thus further our current knowledge of the entire circadian clock.

References:

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