CK1ε: Setting the Clock

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Summary

Phosphorylation, a key post-translational modification of a cell, helps regulate the circadian cycle. An enzyme CK1ε phosphorylates PERIOD tagging the protein for degradation, providing possible treatments for sleep disorders involving CK1ε mutations.

Introduction

Sleep is a vital function of everyday life. In fact, in the United States, fatigue contributes to more than 100,000 highway accidents each year, resulting in 70,000 injuries and 1,500 deaths[1]. Interestingly, about 40% of the U.S. population experiences some form of a sleep disorder annually[1]. The sleep/wake cycle of mammals is controlled by the circadian pacemaker. Thus, the ability of the circadian pacemaker to adapt is crucial to a healthy organism. An incredible study conducted by Meng et al.,[2] determined the molecular mechanism in which a specific enzyme, Casein Kinase 1ε, controls the length of the circadian period.

The circadian pacemaker is a remarkably efficient feedback mechanism found in the suprachiasmatic nuclei of the hypothalamus (SCN)[3]. Although light cues trigger the circadian rhythm, mammals kept in continuous darkness still follow a 24-hour cycle. Shearmen et al., 2000 discovered the protein auto regulatory feedback loop that controls this cycle[4]. They showed that the circadian proteins CLOCK and BMAL1 form heterodimers and act as transcription factors on two other proteins: PERIOD and CRY. PERIOD and CRY, with time, form heterodimers as their concentration increases and eventually inhibit the effects of CLOCK and BMAL1. This is the mechanism that constitutes the circadian cycle. The feedback loop requires help from cells' post-translational modification tools[5]. Although post-translational modifications help the circadian cycle remain consistent, they can disrupt it as well. In 1998, Kloss et al., discovered the first mutation in an enzyme of the circadian cycle, Casein Kinase 1ε, called the *tau* mutation[6]. This mutation substitutes an arginine for a cysteine at the 178th amino acid and decreases the circadian cycle to twenty hours[7]. The role of CK1ε in the circadian cycle and why this mutation causes a decrease in the cycle is still unknown. This prompted Meng et al., to investigate the role of CK1ε and the *tau* mutation. Meng and colleagues hypothesized that CK1ε regulates the circadian cycle via degradation of the PERIOD protein. Also, they believed CK1ε *tau* mutation is gain in function that causes an increase in degradation.

Meng et al.,[2] sought to answer this question by first expressing the CK1ε *tau* mutation in mammals and measuring their circadian cycles. The author reveals that the mutation reduced mice circadian cycles from 23 to 20 hours. Interestingly, however, the knockout mice increased in circadian cycle to 24 hours. The implications of these results are significant because an increase in circadian clock due to a lack of CK1ε indicates the role of regulation that this enzyme has . Furthermore, the decrease in the circadian cycle due to CK1ε *tau* mutation suggests a correlation between the mutation and disruption of the cycle. The next step of this study examined the effect of CK1ε *tau* mutation at the cellular level of the SCN. Firing rates of individual neurons of the SCN were recorded. They found that the firing of individual SCN neurons was decreased in CK1ε *tau* mutant mice. This data implies that the CK1ε *tau* affects neuron's electrical firing rates in the SCN and led the researchers to explore the role of CK1ε in the circadian pacemaker.

Meng et al.,[2] then wanted to examine how CK1ε *tau* mutation functions to disrupt the circadian cycle at the molecular level. Due to previous studies on hamsters, Meng et al., hypothesized that the shortening of the cycle may be due to CK1ε *tau* accelerating the loss of nuclear PERIOD protein. They successfully showed that the mutation caused the amount of PERIOD protein to decline by 50% in four hours while the wild type declined 50% in about five and a half hours. This data suggests that CK1ε *tau* accelerates PERIOD. The acceleration of PERIOD degradation then causes the mice to enter an early nocturnal phase. An excellent addition to this study showed that PERIOD protein was degraded in the presence of CK1ε, but did not degrade in the presence of a control. Additionally, CK1ε *tau* accelerated degradation compared to wild-type CK1ε and had no effect on the degradation of the protein CRY. These results are important because they suggest that CK1ε regulates the circadian cycle specifically through the degradation of PERIOD proteins. This data also indicates that CK1ε *tau* is a gain of function mutation because it accelerates the degradation of PERIOD, thus shortening the circadian cycle.

CK1ε *tau* may be accelerating the degradation of PERIOD, but Meng et al., (2008) still sought to explain why. They next tested for the difference in hypophosphorylated and hyperphosphorylated PERIOD proteins. Results revealed that the hyperphosphorylated PERIOD proteins had a significantly decreased half-life when CK1ε *tau* was present compared to the wild type. This data suggests that hyperphosphorylation of PERIOD is a tag for degradation. CK1ε phosphorylating PERIOD protein as a tag for degradation is consistent with the theory that the mutation is a gain of function. CK1ε *tau* mutation causes hyperphosphorylation of PERIOD and thus accelerates degradation.

The impact of these findings is significant because they bring us closer to the exact, molecular mechanisms of the circadian cycle. Meng and his colleagues have made a huge contribution to the study of the circadian cycle. They found that CK1ε is an important kinase that phosphorylates PERIOD. The phosphorylation of PERIOD tags the protein for degradation. As PERIOD proteins degrade, BMAL1 and CLOCK regain function and the circadian cycle restarts (Figure 1).

In addition, they correctly found that the *tau* mutation of CK1ε is a gain of function mutation that causes hyperphosphorylation of PERIOD and thus accelerates the rate at which it is broken down. Consequently, the *tau* mutation decreases the circadian cycle by initiating the nocturnal cycle early, but not diminishing the length. This data leads researchers toward understanding mutations of PERIOD and CK1ε which have been shown to cause disturbances in the circadian cycle and in sleep, such as familial advanced sleep phase syndrome.[8]

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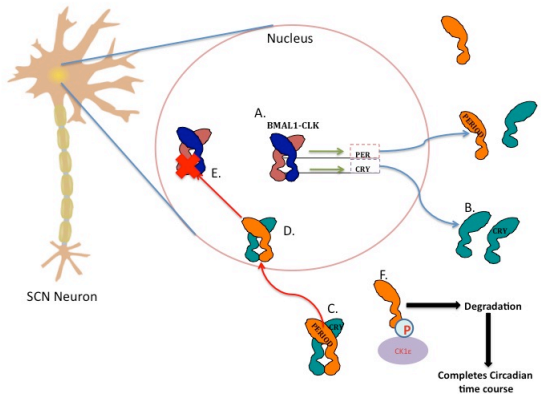

Figure 1: CK1ε helps control the Circadian Cycle. The circadian proteins BMAL1 and CLK are translated in a light dependent manner. A) Together they form a heterodimer that acts as transcription factors for two other circadian proteins: PERIOD and CRY. B) The concentration of CRY and PERIOD increases in the cytoplasm over time. C-D) Once the concentration is sufficient, they form heterodimers and diffuse back into the nucleus. E) Once in the nucleus, the heterodimer inhibits the activity of the BMAL1-CLK heterodimer. F) Over time, Casein Kinase 1ε phosphorylates PERIOD tagging it for degradation. The degradation of PERIOD allows for the circadian cycle to restart.

In the future, these researchers need to continue to work with circadian cycle mutations because there are mutations in multiple key circadian proteins. Other such mutations include a mutation in the PERIOD protein itself that causes familial advanced sleep syndrome[9].

Additionally, research on a similar type of enzyme, CK1*∂*, may be important for circadian mutation, specifically if this kinase is as important to the circadian cycle. Previous research has suggested CK1*∂* in shortening the circadian cycle of mice over expressing PERIOD mutation. CK1*∂* dose dependently decreased the circadian of these mice. Thus, CK1ε might not be the only important kinase in regulating the circadian cycle in humans[10].

As a result of these findings, more research can be done to find treatments to help with mutations in the sleep/wake cycle, and sleep disorders in general. Since, Meng et al.,[2] showed that knocking out CK1ε caused the circadian cycles to slightly increase. Research could potentially target CK1ε and inhibit this protein if a disorder is present. This is why researching the role of other CK1ε enzymes in the circadian cycle is important. If CK1ε is not as important as others, inhibiting the role of this enzyme may help patients inflicted with a sleep disorder while also preventing harmful side effects due to inhibition of an important enzyme.

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