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Functional screening identifies Siah2 as a novel circadian clockwork ubiquitin ligase

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Abstract

Regulated proteasomal degradation of proteins within dynamic cellular pathways is often a critical control point within these pathways. Deregulated protein degradation often leads to cellular dysfunction, and can ultimately cause disease. Thus, identifying the mechanisms underlying degradation of specific proteins holds great potential for identifying novel therapeutic targets in a variety of disease contexts. However, approaches aimed at identifying these mechanisms are limited, hampering discovery efforts. We developed a simple cell-based functional screening approach designed to quickly identify ubiquitin ligases that induce the degradation of potentially any protein of interest. We have begun to use this approach to identify the mechanisms responsible for rhythmic degradation of specific proteins essential to mammalian circadian rhythm generation. These proteins are all rhythmically expressed, however, their degradation mechanisms are not well understood. Initial proof-of-concept screens have revealed that this functional screening is highly specific and capable of identifying novel and physiologically important interactions. This is demonstrated by the identification of Siah2, a RING- type ubiquitin ligase, as a novel regulator of RevErbα stability. We found that Siah2 over expression destabilizes RevErba/b, and siRNA depletion of Siah2 stabilizes endogenous RevErbα. Moreover, Siah2 depletion appears to delay circadian degradation of RevErba, presumably prolonging its activity as a transcriptional repressor, and slowing overall circadian clock function. Overall, our findings suggest that Siah2 is a circadian clockwork E3 ligase that regulates circadian timing by shaping RevErb protein rhythms, and demonstrate the utility of functional screening approaches for identifying regulators of a protein's stability.

Biography

Jason P. DeBruyne earned his Ph.D. from University of Houston (2002), and has followed these with postdoctoral studies at University of Massachusetts Medical School and the University of Pennsylvania School of Medicine. Overall, he has published more than 10 papers in the field of circadian rhythms, including papers in Neuron and Nature Neuroscience. He became an Assistant Professor at Morehouse School of Medicine in 2011, where he is continuing his research on circadian rhythm and sleep mechanisms.