Cell's waste disposal system regulates body clock proteins

October 6 2015

Rhythmic expression of key genes is essential for maintaining proper timekeeping of the body's clock. In addition, rhythmic degradation of clockwork proteins is also crucial. However, surprisingly, researchers know little about these specific processes.

A new Penn-led study describes a new genome screen that identified partner molecules of cell-waste disposal proteins. The team led by John Hogenesch, PhD, a professor of Systems Pharmacology and Translational Therapeutics in the Perelman School of Medicine at University of Pennsylvania and Jason DeBruyne, PhD, a former postdoctoral fellow in the Hogenesch lab and now an assistant professor at Morehouse School of Medicine in Atlanta, applied their new method to identifying other clock partners that target a multipurpose cell nucleus receptor for disposal. Their findings were published online ahead of print in the *Proceedings of the National Academy of Sciences*.

"Our goal was not really to study clock biology," said senior author Hogenesch. "Rather, our aim was to develop a genome-wide screen to identify key players involved in protein stability and breakdown."

The proteins they were looking for are called ligases. These recognize specific proteins and direct the addition of a molecule onto waste proteins to dispatch the protein to be recycled to the proteosome. This is the cell compartment that breaks up used proteins into its basic amino acids.

To validate the screen, the team tagged several of their favorite clock proteins with a short protein tag that's easily recognized by antibodies. The team then used high throughput imaging to see what ligases increase and decrease the levels of their favorite clock proteins in cells. They found that the ligase Fbxl3 was a regulator of Cry proteins, critical components of the core clock. They also found that a protein called Seven in absentia 2 (Siah2) is a key regulator of the turnover of a well-studied, clock nuclear protein called RevErbα on a 24-hour cycle.

Certain ligases, like Fbxl3, can be targeted with small molecules. "These ligases are being actively developed in drug discovery efforts," Hogenesch noted. "Most proteins don't bind with small molecules. With this screen, we may be able to overcome that limitation by finding the ligase that regulates their levels and function. Small molecules against the ligase, then, could indirectly regulate the amount and therefore activity of the 'undruggable' protein."

The researchers hope that by applying this new method, more ligase drug targets can be found and developed into new therapies across the spectrum of health challenges.

Provided by University of Pennsylvania School of Medicine