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The internal clock of cells orchestrates 25 percent of all protein switches

Circadian is the latin meaning for "about a day". Circadian clocks have evolved to adapt our lives to the daily environmental changes on earth: light and warmth during the day and darkness and cold at night. Scientists at the Max-Planck-Institute of Biochemistry in Martinsried discovered with the help of the mass spectrometry, that more than 25 percent of the molecular protein switches in mouse liver cells change in a daily manner. These rhythmic switches are binding sites for phosphate molecules, that regulate the function of proteins, and thereby the daily metabolic processes in the organ. The study was published in the journal *Cell Metabolism.*

Matthias Mann, head of the department "Proteomics and Signal Transduction" at the Max-Planck-Institute of Biochemistry has optimized, together with his research group, the mass spectrometry for use in the clinic over the last few years. This technology enables analysis of proteins both quantitatively and qualitatively in cells and tissue. Additionally, mass spectrometry also enables researchers to study the phosphorylation of proteins - the binding of a phosphate molecule can change the structure and the molecular characteristics of the protein. The phosphate molecule thereby functions like a protein switch, capable of changing the protein activity and function.

This method was used by the scientists to investigate whether the inner clock, the circadian clock, in cells and organs can drive changes of these phosphate switches. Charo Robles, head of the study explains: "The circadian clock is the internal timer in the cell. The rotation of the earth leads to periodic changes of the environment, associated with the day and night that influences living organisms. The inner clock allows organisms to predict the daily fluctuations in the environment and thus adapt the cellular metabolism and physiology.

In the past, it was already discovered that a large proportion of the transcriptome, a set of the messenger RNA molecules and the manual for the proteins, as well as a proportion of the proteins themselves in cells and tissues undergo circadian cyclic rhythms of abundance. This study examined in the circadian changes of the phosphoproteome, the whole set of phosphorylation binding sites in proteins, in the mouse liver.

"While approximately 10 percent of the messenger RNA and the proteins cycle daily in their abundance, we now show that more than 25 percent of the protein switches, phosphorylation

events, change across the day and night to control the function of the proteins in the liver of mice.", says Robles. "As a simple analogy in our daily lives: in the morning we switch the computer when we arrive at work, and switch it off again in the evening, while at home we might switch on the TV in the evening." With the help of mass spectrometry the scientists were able to analyze the complex network of the protein switches. "We do not detect just one switch but rather we can analyze when the different switches are turned on and off in the whole city as analogue of the cell". The scientists showed that around 2,000 phosphorylation positions change between the day and night. Some switches were newly discovered in this study.

With this knowledge, when specific proteins are activated we could promote so called "Chronotherapy". Cellular processes as well as whole organ physiology display cycles of activity across the day. This influences the efficacy and the tolerance of medication. "In the future if we know when in an individual patient specific signaling pathways are activated, we could optimize the treatment of diseases, giving the medication at the appropriate time point to increase efficiency and minimize adverse effects.", says Robles.

Caption:
25 percent of the molecular protein switches are active in the rhythm of the internal clock of a cell. This was shown with the help of the mass spectrometry in the livers of mice.
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