MicroRNAs grease the cell's circadian clockwork

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Most of our cells possess an internal clock, a group of genes displaying a cyclic expression pattern that reaches a peak once a day. A large number of circadian genes are expressed by organs such as the liver, whose activity needs to be precisely regulated over the course of the day.

A team of researchers of the National Centre of Competence in Research Frontiers in Genetics, based at the University of Geneva, Switzerland, reveals that an important regulator of this molecular oscillator is a specific microRNA. The latter belongs to a class of small RNA molecules that regulate the production of proteins in our cells. Thus far, little was known about their function within the circadian clockwork. The study by Ueli Schibler's team, published in the 1st June edition of Genes *& Development*, fills in this important gap.

Living beings have adapted to the alternation between night and day by developing an internal clock, located in the brain. It allows synchronising gene expression and physiological functions with geophysical time. In addition, most of our body's cells possess their own subsidiary oscillators, a group of genes displaying a cyclic expression pattern that reaches a peak every twenty-four hours.

More than 350 genes involved in metabolism, including that of cholesterol and lipids, are expressed in liver cells in a cyclic fashion. Many of them are also influenced by rhythmic food intake. Their activity must therefore be fine-tuned and synchronised with precision to ensure cohesion between diverse metabolic processes.

MicroRNAs induce gene silencing

Ueli Schibler, from the Molecular Biology Department of the University of Geneva, focuses on the mechanisms controlling the tiny oscillators in liver cells. MicroRNAs were among the potential factors likely to be involved in clock gene regulation. The common property of these small molecules lies in their ability to inhibit the synthesis of specific proteins, thus allowing cells to reduce the activity of certain genes at a given time.

"We have studied the role of a microRNA called miR-122, which is highly abundant in liver. It has caught considerable attention for its role in regulating cholesterol and lipid metabolism and in aiding the replication of hepatitis C virus" explains David Gatfield, one of Professor Schibler's collaborators.

Performance of the molecular oscillator…

The researchers' team has discovered that miR-122 is tightly embedded in the output system of the circadian clock in hepatocytes. This microRNA regulates numerous circadian genes, impinging on the amplitude and duration of their expression. Conversely, the synthesis of miR-122 involves a transcription factor that is otherwise known for its function in the circadian clock.

…and viral replication

"It will be exciting to investigate whether the connection between circadian rhythms and miR-122 also extends to this microRNA's role in hepatitis C virus replication", points out David Gatfield. Knowing whether viral multiplication is gated to specific times of the day would contribute significantly to our understanding of the life cycle of this formidable pathogen.

Scientists have uncovered over the past years the role of microRNAs in crucial physiological functions such as growth and programmed cell death, as well as carcinogenesis. Ueli Schibler's team adds a stone to this edifice by placing miR-122 within the clock gene machinery.

Source: Cold Spring Harbor Laboratory (news : web)