UNIVERSITÉ DE GENÈVE

PRESS RELEASE

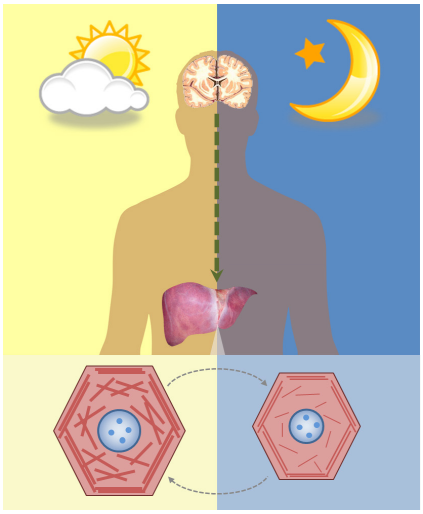
Geneva | 28 January 2013

under embargo until January 31st, 12pm, Eastern Time

IDENTIFYING ALL FACTORS MODULATING GENE EXPRESSION IS ACTUALLY POSSIBLE!

Researchers at UNIGE, Switzerland, develop a screening technique applicable to all areas of basic and clinical research.

It was in trying to answer a question related to the functioning of our biological clock that a team lead by Ueli Schibler, a professor at the University of Geneva (UNIGE), Switzerland, has developed a method whose applications are proving to be countless. The researchers wanted to understand how 'timed' signals, present in the blood and controlled by our central clock, located in the brain, act on peripheral organs. In order to identify gene activator proteins, called transcription factors, involved in this process, they have developed an original screening technique called *Synthetic Tandem Repeat PROMoter (STARPROM)* screening. The biologists thus discovered that the transcription factor called serum response factor (SRF) is activated by the daily variations of a blood signal, resulting in significant changes in the structure and size of liver cells throughout the course of the day. This work, conducted in collaboration with the CHUV in Lausanne and the London Research Institute, is published in the journal *Cell*.



The brain's central clock controls the daily variation of a blood signal (green arrow), which influences the synchronisation of circadian clocks in peripheral organs. In liver cells (hexagons with a nucleus in blue), the blood signal induces significant changes in size and structure, including a reorganization of actin fibres (dark red).

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The biological clock of mammals is made up of a principal «pacemaker» located in the brain, and local oscillators, present in almost all cells. In order for the many functions of our body to be able to fluctuate on a regular basis throughout the course of the day and to maintain phase coherence with each other, the central clock periodically synchronizes the peripheral oscillators by using various signals.

«Our organs always know what time it is. We want to understand how the biochemical signals they receive through the blood are detected and translated in the cells», explains Ueli Schibler, professor in the Department of Molecular Biology in the Faculty of Science at UNIGE. It is already known that systemic signals, produced in a rhythmic fashion in the blood and controlled by the central clock, can stimulate transcription factors in target cells. Each of these proteins binds to specific DNA sequences of the gene it will activate, in a region called the «promoter».

Synthetic promoters produce luminescent signals

Ueli Schibler has a keen interest in the regulation of circadian clocks in peripheral cells. In order to identify the transcription factors solicited in these cells and understand how they function, the researcher's team has developed an original method. «We've built a library of about 850 promoters, having unique characteristics and luminescence markers. Each of these DNA sequences was inserted into a human cell line, before incubating the cells with human plasma collected at different times of the day,» reports Alan Gerber, post-doctoral researcher with the National Center of Competence in Research (NCCR) *Frontiers in Genetics* and first author of the article.

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The biologists thus discovered that daily variations of a plasma signal cyclically stimulate a transcription factor called serum response factor (SRF). SRF activates many genes and is involved in various key processes in cells. Its absence in skin is associated with psoriasis and other skin diseases. «SRF is added to the list of circadian transcription factors. We have also demonstrated that it is solicited in an antiphasic manner in humans and rats, a fact that is linked to their activity, diurnal and nocturnal respectively,» says the scientist.

The cells get larger during the day

«We were very surprised to observe that the liver cells of rodents change their structure during the day, with an average size increase of about 50 percent at the end of the night. SRF activation is accompanied by a remodelling of the cellular «skeleton», resulting in morphological change in cells based on their activity. Previously, it was thought that the cytoskeleton was rather stable, and yet it changes greatly following a circadian rhythm,» explains Ueli Schibler.

The screening technique developed by the researchers, called Synthetic Tandem Repeat PROMoter (STAR-PROM), is a pioneering technology: «The 850 or so elements constituting this library, constructed and screened in a year and a half, should allow us to identify the majority of factors modulating gene expression in a particular context,» says Alan Gerber. Whether in the context of drug treatment, the exploration of a specific signalling pathway, the identification of new regulators, with any stimulus, the applications of this technique are countless.

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