

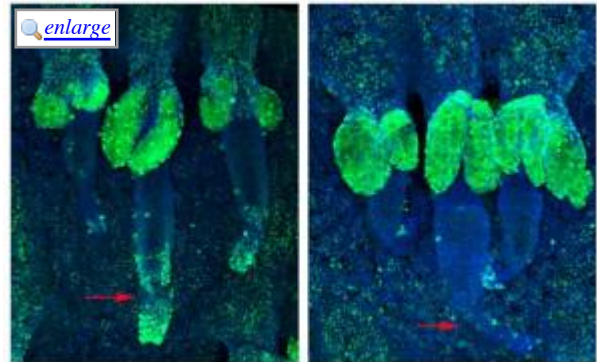
Biological Clock Controls Activation of Skin Stem Cells

ScienceDaily (Nov. 10, 2011) — A new study reveals the role of the daily biological clock (circadian rhythms) in the regenerative capacity of skin stem cells. Disruption of this rhythm results in premature tissue ageing and a greater predisposition to the development of skin tumours. The proper reestablishment of the biological clock increases the long-term regenerative capacity of the tissue and decreases the probability of developing tumours.

Researchers from the Epithelial Homeostasis and Cancer group at the Centre for Genomic Regulation (CRG) have carried out a study which is to be published in the journal *Nature*, describing how circadian rhythms, that is the internal biological clock which controls our behaviour during the day and night, regulate the function of the cells which are responsible for the daily regeneration of the skin (the skin stem cells).

Stem cells regulate cell replacement in tissues. In the case of the skin, they are responsible for constantly producing new cells to replace those that deteriorate through daily use. Correct function of the stem cells is essential for maintaining healthy tissue throughout the life of an organism. The skin is exposed to various harmful agents through the day, such as ultraviolet light during daylight hours, and pathogens such as bacteria and viruses. The main function of the skin is to protect an organism from these potential dangers, whilst being an impermeable barrier separating our body from the outside world.

The researchers involved in the study have found that the behaviour of skin stem cells is regulated by an internal biological clock, and that the correct function of this clock is necessary in order to maintain the tissue. This clock regulates the behaviour of stem cells in such a way that, for example, during the peak hours of light exposure, the cells are able to protect themselves from harmful radiation (the main cause of skin cancer), whilst in the evening and at night they can divide and regenerate the tissue replacing damaged cells with healthy ones. In this way, the biological clock allows stem cells to divide at times when the skin is no longer exposed to possible damage, when it would be more vulnerable to the accumulation of mutations in DNA and which



*Disurbance in circadian rhythm produces an increase of latent cells and a low number of proliferating cells (already differentiated). On the left, many proliferating cells (red arrow) in a sample with active *Bmal1* gene and on the right, very few proliferating cells from a suppressed gene sample. (Credit: Image courtesy of Centre for Genomic Regulation)*

would cause a loss of regenerative capacity, or a higher predisposition to tumour development.

"Therefore, the biological clock enables the precise adjustment of the temporal behaviour of stem cells, in such a way that the system adapts to the needs of the tissue according to the time of day and there is constant replacement of the cells of the tissue with minimal risk of accumulating DNA mutations. If this control is lost, stem cells may accumulate DNA damage, and the likelihood of cell ageing and generation of tumours increases significantly." says Salvador Aznar Benitah, coordinator of the study.

The genes *Bmal1* and *Period1/2* are responsible for controlling this rhythm and regulating cell regenerative activity or rest. Through the genetic manipulation of both genes, the researchers showed that disruption of the biological clock in skin stem cells prevented the cells from knowing when to exercise which function, and that this caused long-term problems in cellular ageing and tissue generation. Moreover, the arrhythmia in the clock also significantly increased the propensity to develop a type of skin cancer which is one of the most commonly diagnosed cancers in industrialised societies.

The biological clock (commonly known as the "circadian rhythm") arranges all of our biological functions according to the natural cycles of light and darkness to which we are exposed on a daily basis. The results of the group from the Centre for Genomic Regulation show that skin regeneration, essential to prevent from ageing and tumour development, is also subject to these rhythms. As we age, the accuracy of this biological clock tends to fade gradually with changes in our daily routine, specially with those who are exposed to constant changes like jet lag in frequent flyers. Researchers believe this may eventually cause failure in the regenerative capacity of our tissues and consequent ageing, and, in addition, a greater propensity to tumour development. More research will be needed in the future to understand why the biological clock fades as we age, and whether ways to restore a "young" clock can be developed to slow down the tissue degeneration process and reduce the risk of developing tumours.

The study was carried out using mouse skin cells, with the support of the American Institute for Cancer Research (AICR), the Spanish Ministry of Health and the Agency for Management of University and Research Grants (AGAUR). The study involved researchers from the IRB in Barcelona, Ohio State University in the USA and the University of Fribourg in Switzerland.

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Journal Reference:

1. Peggy Janich, Gloria Pascual, Anna Merlos-Suárez, Eduard Batlle, Jürgen Ripperger, Urs Albrecht, Karl Obrietan, Luciano Di Croce, Salvador Aznar Benitah. **The circadian molecular clock creates epidermal stem cell heterogeneity.** *Nature*, 2011; DOI: [10.1038/nature10649](https://doi.org/10.1038/nature10649)

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