Research team shows skin stem cells run by circadian clock

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(PhysOrg.com) -- Most everyone has heard of the circadian rhythm or the internal clock that people have that tells them when to do things, such as go to sleep. In fact, researchers have actually located where this "clock" resides in the human brain. It's in the suprachiasmatic nuclei, a pair of distinct groups of cells located in the hypothalamus. So, that would seem the end of it right, except it's not; new research by a group in Spain has found that individual stem cells in skin have their own circadian clock of sorts that tells the skin when to do certain thing, like regenerate. The team led by Peggy Janich and Salvador Aznar Benitah, has published the results of their study in *Nature*.

Janich, Benitah, et al, knew that mice grew new skin cells mostly at night, but weren't sure how exactly that came about. To find out they studied a protein produced in the skin called Per1, which they suspected had clock-like abilities and that it impacted the expression of signaling proteins which tell other cells when to start doing their thing - such as growing new cells. To see what it was doing they linked the Per1 cell with another protein that goes fluorescent when exposed to certain environmental factors. This allowed them to see when the Per1 cells were active or dormant. In watching the cells they found they oscillated over regular 24 time period. They also found that the amount of brightness shown by the fluorescent protein correlated directly with the amount of signaling protein expressed.

Furthermore, the group found that the Per1 cells appear to be regulated, at least in part, by the main body clock in the brain. This they found out

by removing a clock protein called Bmal1 from the test mice. In its absence, the Per1 cells failed to adhere to their circadian rhythm.

The researchers note that the skin in particular is more sensitive to external stimuli than many other body parts, due to its external nature. Thus, nature has had to allow for constant adjustment to keep it functioning properly. In this case, it appears the skin stem cells need to do different things during different times of the day. In the morning for example, new skin cells grown overnight need to replace those that have died. And the reason new skin cells grow at night is because that is when they are least susceptible to UV rays that can cause skin cancer.

Unfortunately, the authors note, it's not quite as simple as all that because sometimes cells that are supposed to be timed by Bmal1 proteins seem to ignore them, and other times seem to act independently, thus leading to the conclusion that there are more factors at work in the timing of cell replication than just the circadian rhythm. Thus, as always, more research into how skin stem cells are regulated will need to be done to find out why this happens and what can be done about it in the situations where they lead to cancers.

More information: The circadian molecular clock creates epidermal stem cell heterogeneity, *Nature* (2011) doi:10.1038/nature10649

Abstract

Murine epidermal stem cells undergo alternate cycles of dormancy and activation, fuelling tissue renewal. However, only a subset of stem cells becomes active during each round of morphogenesis, indicating that stem cells coexist in heterogeneous responsive states. Using a circadian-clock reporter-mouse model, here we show that the dormant hair-follicle stem cell niche contains coexisting populations of cells at opposite phases of the clock, which are differentially predisposed to respond to homeostatic cues. The core clock protein Bmal1 modulates the

expression of stem cell regulatory genes in an oscillatory manner, to create populations that are either predisposed, or less prone, to activation. Disrupting this clock equilibrium, through deletion of Bmal1 (also known as Arntl) or Per1/2, resulted in a progressive accumulation or depletion of dormant stem cells, respectively. Stem cell arrhythmia also led to premature epidermal ageing, and a reduction in the development of squamous tumours. Our results indicate that the circadian clock fine-tunes the temporal behaviour of epidermal stem cells, and that its perturbation affects homeostasis and the predisposition to tumorigenesis.