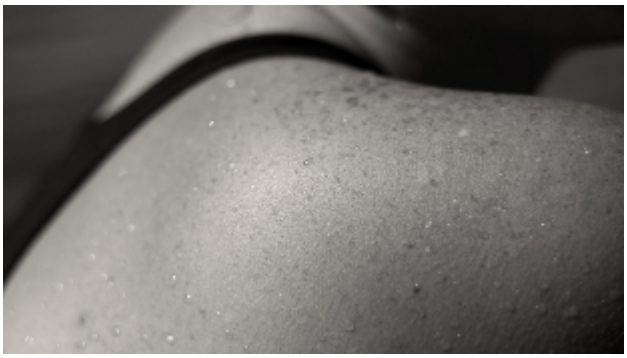
News & Opinion

How Skin Tells Time

The behavior of skin stem cells is regulated by a 24-hour circadian clock.

By Ruth Williams | November 9, 2011



Flickr, Ted Goldring

Stem cells in the skin, which are responsible for replacing dead skins cells that are continuously sloughed off, follow a daily rhythm that is under the control of a 24-hour circadian cycle, according to a study published today (November 9) in *Nature*.

"It was known that in mice [skin] proliferation occurs mostly in the night," said Salvador Aznar-Benitah of the Centre de Regulació Genòmica in Barcelona, Spain, who led the study. "Now that we have added the molecular mechanism we know that this is purely regulated by circadian rhythms."

"This is a very exciting paper because it links what we knew about signaling molecules [in skin stem cells]…to a much more global regulation—the circadian clock," said Valentina Greco of Yale University, who was not involved in the study. "It reconciles much of the fragmented information we had," she said.

Aznar-Benitah and his colleagues examined the regulation of a known clock protein, Per1, in mouse skin stem cells using a fluorescent protein linked to the clock protein's promoter. As is the case in other cells of the body, the level of fluorescence oscillated over a 24-hour period.

Furthermore, the levels of proliferation-promoting signaling proteins corresponded with the level of the fluorescence—in cells where the fluorescence was bright, proliferation proteins were highly expressed. In dimly fluorescing cells, on the other hand, the expression of such proteins was low.

This suggested that the body's central clock regulates expression of the signaling proteins in skin, and possibly proliferation. Sure enough, in mice whose skin cells lacked a clock protein called Bmal1, the expression of the signaling molecules was reduced, as was the proliferation of skin stem cells.

"The clock is timing the function of skin cells," said Aznar-Benitah. "So for example, it is telling the skin that in the morning the main function it has to do is to deal with UV radiation." Skin stem cells tend to replicate their DNA later in the day to avoid UV-induced mutations, he explained. Indeed, the overall reduction in proliferation in the Bmal1-deficient mice protected them from developing skin cancers.

"This [paper] provides another line of evidence that the clock machinery regulates the protection and activation of the skin cells," said Cedric Blanpain of the Université Libre de Bruxelles in Belgium, who was not involved in the study. "It has very interesting implications for tumorigenesis," he added. For example, "if you are jet-lagged and you go into the sun immediately, your cells are much less prepared."

Although expression of the clock ensures the correct timing of proliferation, many stem cells expressing Bmal1 do not actually replicate. Stem cells in the hair follicle, for example, go through long periods of dormancy where almost no cell proliferation occurs, despite the fact that approximately 50 percent of these cells express the clock proteins. Of these clock-expressing cells, "only 10-20 percent of them actually become active every day," said Aznar-Benitah. Similarly, only 30-40 percent stem cells outside the follicles replicate each day, though almost all of them express clock proteins, Aznar-Benitah explained.

"The clock is therefore not deterministic but just adds a factor of predisposition to the equation of stem cell activation," said Aznar-Benitah, "The actual activation depends on the clock and on several other factors—i.e. receiving the activating stimulus." For skin stem cells, the exact nature of this stimulus is currently unknown.

Also unknown is why only some skin stem cells express the clock molecules. "We were really intrigued, and still are, about this finding," said Aznar-Benitah. "We have some indication that in fact the 50 percent of [follicle] cells that are not positive [for clock proteins] might not even be cycling at all, which raises the question of how can a cell be clock-less."

P. Janich et al., "The circadian molecular clock creates epidermal stem cell heterogeneity," ***Nature,*** **doi:10.1038/nature10649, 2011.**
