Mouse and human skin cells produce melanin on a 48-hour cycle

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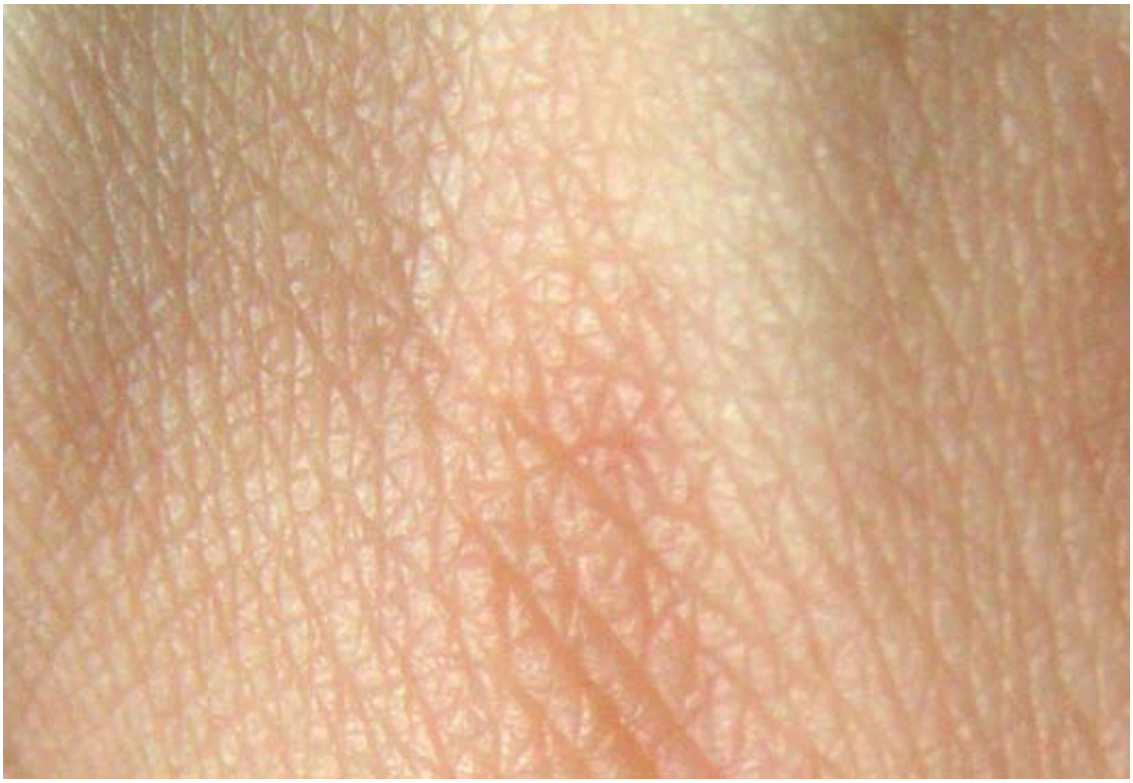

Human skin structure. Credit: Wikipedia

Researchers have discovered that mouse skin and skin cells from humans produce pigmentation in response to sunlight on a 48-hour cycle. They observed that exposing skin to ultraviolet light every 2 days yielded darker pigmentation with less radiation damage than daily exposure. The findings appear October 25 in the journal *Molecular Cell*.

"The damaging effects of high doses of ultraviolet rays are known, but we were curious to see the effect of exposure frequency on skin," says senior author Carmit Levy, a molecular geneticist at Tel Aviv University. "It turns out that, if you are going out daily to the beach, you might be interfering with the natural scheduling and synchronizing of the skin protection systems."

The skin responds to ultraviolet light, the high-energy light that makes up a fraction of the sun's rays, in two ways: first, by inflaming and triggering an immune response, repairing radiation-induced DNA breakage, and multiplying its cells to protect the more delicate underlying layers. And second, by producing melanin, a brown-to-black pigment in skin, eyes, and hair, that tans the skin and acts as natural sunscreen for the next exposure. Stress responses to ultraviolet light initiate within minutes, while melanin production can take hours or days to start.

Levy's team, led by Tel Aviv University Ph.D. student Hagar Malcov-Brog, wanted to understand how the timing of the skin's two protection programs relate to each other. They exposed live mice to ultraviolet exposure every day, every other day, and every 3 days. Then they measured the amount of melanin with a color meter and counted the number of DNA breakages in the skin cells. They observed that a 48-hour cycle of exposure resulted in the darkest coloration of the cells while minimizing the effects of stress, even when they controlled for total dosage of exposure.

"The results were so surprising," says Levy. "We expected daily synchronization of the cell's protective cycles."

Levy and her colleagues, including co-senior author and systems biologist Shai Shen-Orr and his Ph.D. student Avelet Alpert of the Technion—Israel Institute of Technology, observed that MITF

(microphthalmia-associated transcription factor) seemed to play a role in synchronizing the protective cycles. MITF was previously shown to control production of melanin and its spread to surrounding skin cells. They found that upon one ultraviolet exposure, MITF expression fluctuates every 48 hours. Another exposure 24 hours later seemed to disrupt this expression pattern.

Levy's team next carried out a comparable experiment in pigmented human cells derived from a cancerous cell line but approved as a model for pigment production in non-cancerous cells. Ultraviolet exposure can only activate melanin production in the presence of other skin cell types, so they had to mimic ultraviolet radiation's effect on the cultured cells. Thus, they directly stimulated MITF activity in the cultured cells using a downstream regulator. They found that a 48-hour cycle of stimulation produced the most pigmentation in the human cells while minimizing stress-induced proliferation.

Levy's team speculates that the 48-hour cycle arose in ancient humans when we lost our protective fur, which many believe occurred when we descended from the trees and began to walk around on two feet. Others have theorized that we lost our fur as a response to the Savannah heat, for hygienic purposes, or by sexual selection.

"We also began to express an important receptor for pigment production in our skin, called MC1R, at that time," says Levy. "Evolving coordinated action of programs—in other words, linking traits—in response to a common selective pressure can grant an adaptive advantage. However, we're not sure why we would have evolved for a 48-hour cycle when ancient humans were probably exposed to the sun every day. We do know that vitamin D, which the skin produces upon exposure to the sun, is stable in the blood for 48 hours post-exposure. Perhaps there is a link."

The team believes that understanding transcription factor dynamics may lead to crucial insights for correctly timing skin cancer treatments, some of which have been previously shown to be frequency dependent. Their results would need to be replicated in human trials before any claims could be made about their therapeutic potential, or even simply about safer tanning habits.

"We will continue to study these cycles, and we would like to better understand the effect of ultraviolet exposure on the proteins in our cells and bloodstream," says Levy. "I think there are more 'clocks' in our body to discover."

More information: *Molecular Cell*, Malcov-Brog et al.: "UV-protection timer controls linkage between stress and pigmentation skin protection systems." www.cell.com/molecular-cell/fu … 1097-2765(18)30793-7 , DOI: 10.1016/j.molcel.2018.09.022

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