Scientists identify key mechanism controlling skin regeneration

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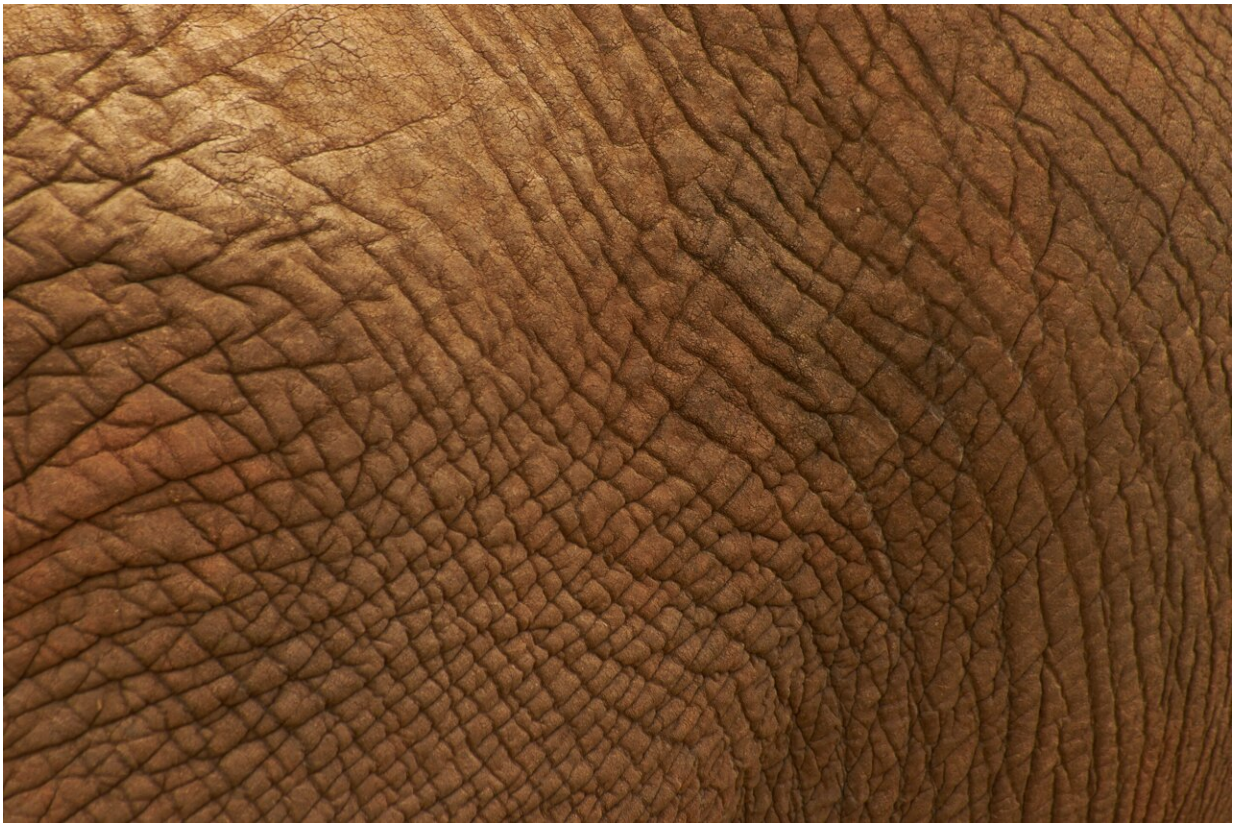

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It's sunburn season. Many of us have experienced the pain and peeling that comes from unprotected time in the sun, but we may not focus on a remarkable and vital part of the process: the regeneration of skin as the

damaged tissue is replaced with new.

Even without sunburn, the outer layer of skin, the epidermis, is constantly turning over to replace dead or damaged cells throughout our lifetime. This epidermal layer provides an essential barrier for the human body, reducing water loss and combating environmental threats. Scientists are working to identify the molecular mechanisms controlling skin epidermal regeneration, but much remains poorly understood.

Now a Northwestern University research team has identified a molecular switch, through a protein called CDK9, that plays an early and critical role in the skin stem cell differentiation process. This switch is "off" in the stem cells. When the switch is turned on, a specific group of genes is immediately activated to trigger downstream gene regulators, allowing the skin cells to progressively gain barrier function. The findings have relevance for improved understanding of cancer and wound healing, in addition to the fundamental understanding of skin regeneration.

"Skin stem cells need to continuously make decisions, to either make more copies of themselves—a process known as self-renewal—or to switch their fate towards differentiation. A delicate balance between these two decisions is crucial to maintain the integrity of skin and its barrier function," said Xiaomin Bao, a stem cell biologist at Northwestern who supervised the research. "We have discovered the switch bound to selected genomic regions inside the stem cells, ready to trigger the cell fate switch of initiating the stem cell's movement towards differentiation."

Bao is an assistant professor of molecular biosciences in the Weinberg College of Arts and Sciences and an assistant professor of dermatology at Northwestern University Feinberg School of Medicine. Her lab studies the fundamental biology of the process of skin stem cell differentiation.

The study was published recently by the journal *Nature Communications.*

Discovery of the switch

The integrity of skin epidermis relies on subsets of skin stem cells to continuously self-renew or differentiate, compensating for daily wear and tear. The differentiation process involves significant changes from more than 6,000 genes, ceasing stem cell proliferation while activating barrier-function genes.

Integrating genomics, genetics and pharmacological inhibition to human skin models, Bao and her team identified that the kinase activity switch of the protein CDK9 plays a key role in the decision of cells to initiate differentiation and progressively acquire the barrier function of the tissue. The kinase activity is off in the stem cell state, and the rapid-response genes directly controlled by the kinase are suppressed. When the kinase activity is on, the rapid-response genes are activated, which subsequently induce the downstream effectors, a group of transcription factors that can further drive the expression of barrier-function genes.

CDK9 (cyclin-dependent kinase 9) plays crucial roles in modulating gene expression at the step of "transcription," a process of copying specific DNA regions to RNA, before RNA can serve as templates for synthesizing new proteins. In the stem cell state, CDK9 is maintained in the "off" state when bound together with the proteins AFF1 and HEXIM1 on DNA, awaiting specific cellular signals such as the activation of protein kinase C signaling. Once the signaling is activated, this is sufficient to switch CDK9 from the inactive to the active state, allowing the rapid synthesis of RNA from the genomic regions directly bound by CDK9, the researchers found.

The switch is a quick one. "All the components are poised for action deep inside the stem cells," Bao said. When the stem cell receives

specific external signals, the response inside the nucleus is very fast, with activated CDK9 quickly causing rapid-response genes such as ATF3 to be expressed within as short as one hour. The expression of ATF3 potently induces several downstream transcription factors to rewire the cell fate towards differentiation. This quick switch for gene activation is also built upon the pre-recruitment of RNA-synthesis machinery together with CDK9 to the rapid-response genes, before the signaling is activated.

"We are probing the unknown," Bao said. "Stem cell regulation is fundamental for sustaining the integrity of human tissue. We have found a key mechanism initiating the fate switch of skin stem cell towards differentiation, an integral process of regeneration. Learning more about the fundamental molecular mechanisms can help in the understanding of many different human diseases."

Bao also is a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

The title of the paper is "CDK9 activity switch associated with AFF1 and HEXIM1 controls differentiation initiation from epidermal progenitors." Bao is the corresponding author. Sarah M. Lloyd, an IBiS Ph.D. student in Bao's lab and an awardee of the Northwestern TGS Presidential Fellowship, is the paper's first author.

More information: Sarah M. Lloyd et al, CDK9 activity switch associated with AFF1 and HEXIM1 controls differentiation initiation from epidermal progenitors, *Nature Communications* (2022). DOI: 10.1038/s41467-022-32098-2

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