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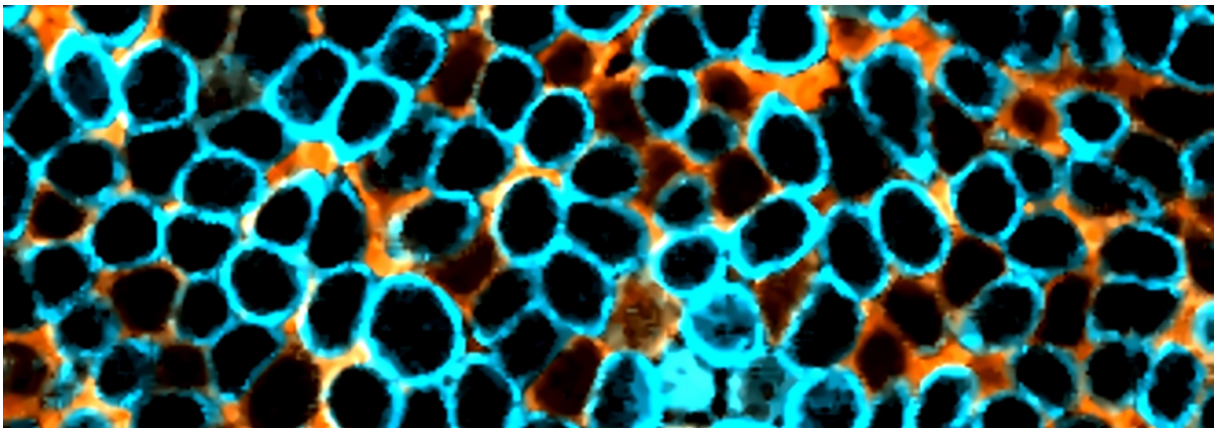

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Skin has a sex: females and males do not renew their skin in the same way

Published in Nature: by filming skin stem cells in living mice over five months, researchers at the Université libre de Bruxelles (ULB), in collaboration with the University of Cambridge, have discovered that in females these cells renew the skin in a more coordinated way than in males. This difference, controlled by sex hormones, goes hand in hand with faster wound healing in female mice. This research could eventually pave the way for future personalized treatments taking into account patients' sex.

For a long time, differences between females and males were mainly associated with the reproductive organs. Yet organs that have nothing to do with reproduction, such as the skin, can also be shaped by sex. This question, essential for better preventing and treating inflammatory diseases and cancer, has long been underestimated by part of the scientific community.

The study, published in the prestigious journal Nature, was led by Prof. Cédric Blanpain, MD/PhD, investigator at the WEL Research Institute, director of the Laboratory of Stem Cells and Cancer and professor at the Université libre de Bruxelles, in collaboration with the team of Prof. Benjamin Simons at the University of Cambridge and other partner institutions.
The researchers used a microscopy technique that makes it possible to film cells through the skin of a living mouse. They were thus able to follow the same stem cells and their descendants for five months, an unprecedented tracking period. Having set out to understand how the skin renews itself, they uncovered an unexpected difference between females and males and then showed that sex hormones are responsible for it.

How the skin renews itself

The outer layer of the skin is constantly being renewed. At the very bottom lie the stem cells, which multiply. Some of their "daughter" cells remain stem cells; others become specialized skin cells that ensure the skin barrier function and are incapable of division (a process called differentiation), move up towards the surface and are eventually shed.
How this process is organized has been debated for decades. By filming the same areas of skin for five months, the team showed that stem cells do not turn directly into mature skin cells: they first go through an intermediate stage, during which they can only divide a limited number of times, before becoming fully specialized.

In females, stem cells are highly synchronized

Even more surprisingly, in females two "sister" cells, born from the division of the same cell, tend to make the same choice at the same time: to divide again or to specialize. Like two rowers synchronizing their strokes, they move in step. In males, each cell follows its own rhythm to a greater extent.
"We initially set out to understand how the skin renews itself, and whether there is a hierarchy with stem cells at the top. We were surprised to discover strong differences in the way stem cells renew the skin in females and males," explains Doctor Dan Engelman, the first author of the study.

Sex hormones set the tempo

To understand where this difference comes from, the researchers turned to sex hormones. Castration of male mice, which removes the main source of male hormone called testosterone, showed that male sex hormones control the speed at which skin cells differentiate and leave the stem cell layer: after castration, male skin behaves more like female skin, whereas treatment with dihydrotestosterone (DHT), an active form of testosterone, restores the male behaviour. Conversely, removal of the ovaries (ovariectomy) in females reduces stem cell proliferation, an effect reversed by treatment with oestradiol, the female hormone, and almost abolishes the signature of coordination between sister cells.
In short, testosterone, which is more abundant in males, controls the rate of skin cell maturation, whereas oestrogens, which are more abundant in females, drive stem cell proliferation and contribute to their coordination.
Finally, in human skin reconstructed in the laboratory, testosterone also accelerates stem cell differentiation, suggesting that this mechanism also exist in humans.

Faster wound healing in females

The researchers also observed that a wound on the skin of the back closes markedly faster in female mice, especially during the first few days. This head start is partly explained by an earlier

activation of stem cells, which also work in a more coordinated way. The gap then narrows as the wound closes.

Why it matters

Doctors and researchers have long observed that wound healing, the severity of certain inflammatory diseases and the frequency of certain skin cancers differ between men and women, without really understanding why. By identifying cellular and hormonal mechanisms behind these differences in the skin, this study lifts part of the veil.
In the long run, it could pave the way for treatments that take the patient's sex into account, for example for burns, recovery after surgery or chronic wounds in people with diabetes, which affect millions of people worldwide. It could also inspire new strategies to prevent skin cancers, which are extremely common.

These results also shed light on a long-standing debate among specialists about how the skin renews itself.

"This study is a technological tour de force, and the discovery of differences between male and female skin stem cells is fascinating and entirely unexpected. It sheds light on a series of clinical observations that previously lacked a biological explanation. It opens up a wide range of new questions, spanning from fundamental stem cell biology to clinical issues such as wound healing, cancer development, and autoimmune diseases. Sex is a parameter too often overlooked in biology and medicine. We will now investigate the differences between males and females during the formation and progression of skin cancers, as well as the molecular mechanisms responsible for these differences" says Prof. Cédric Blanpain, who led the study.

Collaborations and funding

This study is a collaboration between the team of Prof. Blanpain (ULB, Belgium) and that of Prof. Simons (University of Cambridge, UK), with the teams of Michele De Luca (University of Modena and Reggio Emilia, Italia), Yulia Shwartz (Broad CIRM Center, University of Southern California, Los Angeles, US) and Esther Hoste (VIB-Ghent University, Belgium).
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Reference

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