

Aging reprograms skin genetic activity and promotes inflammation

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Researchers at IRB Barcelona identify a molecular mechanism that amplifies chronic inflammation in aged skin.

- With age, two proteins that normally help maintain epidermal function, BMAL1 and YAP, switch to promoting genes associated with inflammation.
- The study, conducted mainly in mice and supported by the analysis of human skin data, has been published in the journal *Nature Aging*.

As we age, the skin loses part of its ability to regenerate, heal wounds, and maintain an effective barrier against the outside world. Among the causes of this deterioration is a low-grade, persistent age-associated inflammation, but the mechanisms that keep this response active in skin cells are not yet well understood.

A study led by **Dr. Guiomar Solanas**, now at the Institut de Recerca Sant Joan de Déu, Pediatric Cancer Center Barcelona, and **Dr. Salvador Aznar Benitah** describes a molecular mechanism that explains this process. During ageing, two proteins called BMAL1 and YAP change the way they work together and increase the activity of inflammatory genes in the epidermis, the outermost layer of the skin. The work has been published in the journal *Nature Aging*.

"Our results show that, during ageing, mechanisms that normally maintain epidermal homeostasis change function and begin to amplify inflammation," explains **Dr. Salvador Aznar Benitah**, ICREA researcher and head of the Stem Cells and Cancer laboratory at IRB Barcelona.

A machinery that changes function

BMAL1 is known for being part of the circadian clock, which coordinates numerous processes in the body throughout the day. For its part, YAP helps cells adapt to physical changes in their environment. The study reveals that both proteins collaborate in the epidermis independently of daily rhythms. In adult skin, this collaboration contributes to preserving the identity and proper function of skin cells.

What happens with age is that changes in skin stiffness, together with an increase in inflammatory signals, cause both proteins to concentrate in regions of DNA that control inflammatory genes and increase their activity.

From IL-17 to the skin cell response

The finding provides continuity to a study from the same laboratory, published in 2023. In that work, the team identified IL-17 as a key inflammatory signal in skin ageing. In mice, temporary blockade of this protein reduced persistent inflammation and delayed some features associated with skin ageing.

The new research shows what happens inside epidermal cells when they receive this signal, which originates from immune cells in the dermis (the deeper layer of the skin). According to the

experiments, IL-17 contributes to the activation of YAP. When the team blocked IL-17 in aged mice, YAP-associated activity and the expression of the inflammatory genes studied also decreased.

"In 2023, we identified IL-17 as a key signal in skin ageing. Now we have discovered how epidermal cells respond to that signal and amplify inflammation," explains **Júlia Bonjoch**, first author of the study.

The finding clarifies how ageing and inflammation are connected in the skin. The next step will be to explore whether this mechanism can be safely regulated without compromising essential functions of the epidermis.

Researchers from the Max Planck Institute for Molecular Biomedicine in Münster, Germany, also participated in this study. The research was funded by the European Research Council, the Government of Spain, the Generalitat de Catalunya, the Fundació La Marató de TV3, the Fondation Bettencourt Schueller, the Spanish Association Against Cancer, and Worldwide Cancer Research, among other entities.

Related article:

Non-circadian BMAL1-YAP activity amplifies persistent inflammation in aged epidermis

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