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Hair-raising research: Scientists find surprising link between immune system, hair growth

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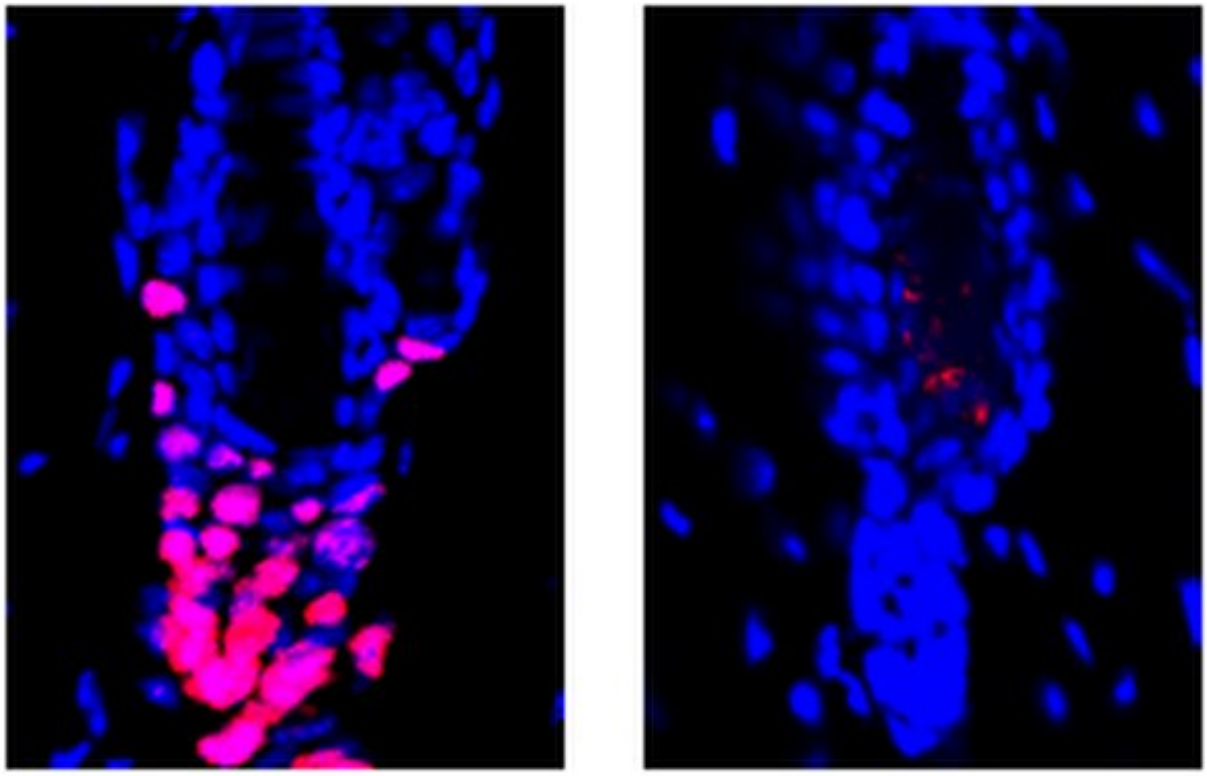

Glucocorticoid hormone signal in regulatory T cells promotes hair follicle stem cell activation and new hair growth. Left: After hair loss, skin cells (blue) from a normal mouse can activate hair follicle stem cells (red). Right: Cells from mice without glucocorticoid receptors in their regulatory T cells cannot activate hair follicle stem cells. Credit: Salk Institute

Salk scientists have uncovered an unexpected molecular target of a common treatment for alopecia, a condition in which a person's immune system attacks their own hair follicles, causing hair loss. The findings, published in *Nature Immunology* on June 23, 2022, describe how immune cells called regulatory T cells interact with skin cells using a hormone as a messenger to generate new hair follicles and hair growth.

"For the longest time, regulatory T cells have been studied for how they decrease excessive immune reactions in autoimmune diseases," says corresponding author Ye Zheng, associate professor in Salk's NOMIS Center for Immunobiology and Microbial Pathogenesis. "Now we've identified the upstream hormonal signal and downstream growth factor that actually promote hair growth and regeneration completely separate from suppressing immune response."

The scientists didn't begin by studying hair loss. They were interested in researching the roles of regulatory T cells and glucocorticoid hormones in autoimmune diseases. (Glucocorticoid hormones are cholesterol-derived steroid hormones produced by the adrenal gland and other tissues.) They first investigated how these immune components functioned in multiple sclerosis, Crohn's disease and asthma.

They found that glucocorticoids and regulatory T cells did not function together to play a significant role in any of these conditions. So, they thought they'd have more luck looking at environments where regulatory T cells expressed particularly high levels of glucocorticoid receptors (which respond to glucocorticoid hormones), such as in skin tissue. The scientists induced hair loss in normal mice and mice lacking glucocorticoid receptors in their regulatory T cells.

"After two weeks, we saw a noticeable difference between the mice—the normal mice grew back their hair, but the mice without glucocorticoid receptors barely could," says first author Zhi Liu, a

postdoctoral fellow in the Zheng lab. "It was very striking, and it showed us the right direction for moving forward."

The findings suggested that some sort of communication must be occurring between regulatory T cells and hair follicle stem cells to allow for hair regeneration.

Using a variety of techniques for monitoring multicellular communication, the scientists then investigated how the regulatory T cells and glucocorticoid receptors behaved in skin tissue samples. They found that glucocorticoids instruct the regulatory T cells to activate hair follicle stem cells, which leads to hair growth. This crosstalk between the T cells and the stem cells depends on a mechanism whereby glucocorticoid receptors induce production of the protein TGF-beta3, all within the regulatory T cells. TGF-beta3 then activates the hair follicle stem cells to differentiate into new hair follicles, promoting hair growth. Additional analysis confirmed that this pathway was completely independent of regulatory T cells' ability to maintain immune balance.

However, regulatory T cells don't normally produce TGF-beta3, as they did here. When the scientists scanned databases, they found that this phenomenon occurs in injured muscle and heart tissue, similar to how hair removal simulated a skin tissue injury in this study.

"In acute cases of alopecia, immune cells attack the skin tissue, causing hair loss. The usual remedy is to use glucocorticoids to inhibit the immune reaction in the skin, so they don't keep attacking the hair follicles," says Zheng. "Applying glucocorticoids has the double benefit of triggering the regulatory T cells in the skin to produce TGF-beta3, stimulating the activation of the hair follicle stem cells."

This study revealed that regulatory T cells and glucocorticoid hormones are not just immunosuppressants but also have a regenerative function.

Next, the scientists will look at other injury models and isolate regulatory T cells from injured tissues to monitor increased levels of TGF-beta3 and other growth factors.

More information: Ye Zheng, Glucocorticoid signaling and regulatory T cells cooperate to maintain the hair-follicle stem-cell niche, *Nature Immunology* (2022). DOI: 10.1038/s41590-022-01244-9. www.nature.com/articles/s41590-022-01244-9

Provided by Salk Institute