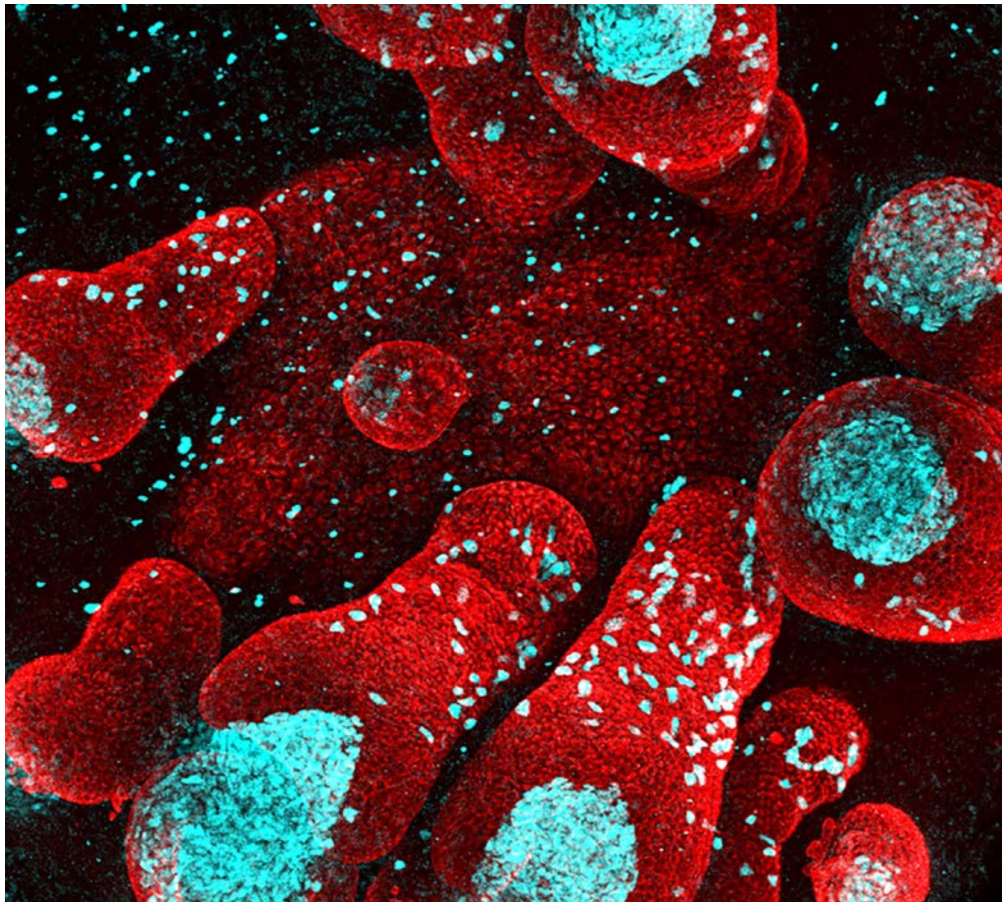
Hair-growing skin produced from human stem cells

Complete skin-in-a-dish tissue offers new options for wound healing, genetic skin conditions and baldness.



A stem cell-derived human skin organoid with sprouting hair follicles (red) with dermal papilla cells (cyan) after three months in culture.

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A new procedure enables researchers to generate skin from undifferentiated cells. As well as a tool for studying how skin develops, these skin organoids could be used as a source for grafts as well as for screen and testing drug treatments.

Skin is the body's largest organ. It is also multi-layered and multi-functional, acting as a protective barrier, helping to control body temperature and mediating sensation. Although outer-layer skin cells have been grown in laboratories for decades, scientists had previously not been able to recreate this organ, with its follicles and glands, in a dish.

Now, Karl Koehler at Boston Children's Hospital, United States, and his colleagues, have managed to generate skin organoids by directing the differentiation of human pluripotent stem cells in a 3D culture system.

Because the cells that form the main layers of skin (epidermis and dermis) are derived from different cell types in the early embryo, the authors first had to optimise the growth conditions. The sequential addition of growth factors triggered the differentiation of human pluripotent stem cells into non-neural ectoderm. This gave rise to epidermal cells, and cranial neural crest cells, which gave rise to cells of the dermis in the face.

After the cells grew for 70 days as spherical aggregates, the first hair follicles were observed on the surface along with some associated tissues such as sebaceous glands, nerves, muscles and fat. "We were truly astounded to see hair growing in our culture dish," says Koehler. "As we repeated the experiments we learned how the process closely mimics the sequence of human fetal skin development."

To further investigate the cellular composition of the skin organoids, the team performed single-cell RNA sequencing at various time points. They identified four main cell subtypes, but found them in slightly different proportions between organoids. Despite this variability, the gene expression signatures indicate that the organoids mimic facial skin. Tweaking the protocol could generate skin with the characteristics of other body parts and could shed new light on the mechanisms involved in skin growth.

To explore the therapeutic potential of these skin organoids, the authors transplanted them on to immunodeficient mice. Just over half of the grafts sprouted hair, highlighting the exciting possibility of using skin organoids for healing wounds or producing hair in bald scalps.

The authors also point out that skin organoids generated from patients with genetic skin disorders or skin cancers could be used to screen for drug efficacy and toxicity, accelerating the discovery of new treatments.

"The next steps will be to better understand how skin organoids might react with a patient's immune system," says Koehler. "The path to the clinic is going to be challenging, but these early results are quite promising."

Lee, J., Rabbani, C.C., Gao, H. *et al.* Hair-bearing human skin generated entirely from pluripotent stem cells. *Nature* **582**, 399–404 (2020).