News & views

Regenerative medicine

Hair-bearing skin grown in a dish

Leo L. Wang & George Cotsarelis

Undifferentiated human stem cells have been coaxed to develop into skin-like structures *in vitro*. When engrafted onto mice, the structures produce hair – highlighting the potential of the approach for regenerative therapies. **See p.399**

When hair follicles were first generated from stem cells that had been isolated from adult mouse skin[1], Jay Leno – a former host of US talk show *The Tonight Show* – joked that scientists "cured baldness ... at least in mice". Sixteen years on, the current host will have the opportunity to mention that scientists have 'cured' baldness in humans, now that Lee *et al.*[2] (page 399) have regenerated hair follicles from human stem cells. This achievement places us closer to generating a limitless supply of hair follicles that can be transplanted to the scalps of people who have thinning or no hair. Moreover, if the approach reaches the clinic, individuals who have wounds, scars and genetic skin diseases will have access to revolutionary treatments.

Research into skin-tissue engineering began in 1975, when a landmark study showed that cells called keratinocytes could be isolated from the surface layer of a person's skin (the epidermis)[3], and the cell population expanded in culture. Almost a decade later, sheets of keratinocytes isolated from people with burns were transplanted back to the individuals they came from as life-saving, permanent engraftments[4]. This work was the foundation for another remarkable achievement in 2017, when a boy who had a genetic disease called junctional epidermolysis bullosa (which causes severe fragility of the skin) had his epidermis replaced with genetically corrected cells[5]. For this type of cell-based approach to advance further, grafted skin must include more of the components found in normal skin: hair follicles, pigment-producing melanocyte cells, sweat glands, nerves, muscle, fat and immune cells, in addition to epidermal cells.

Enter Lee and colleagues. The authors leveraged research from the fields of stem-cell biology and hair-follicle development[6] to generate near-complete skin organoids – self-organizing tissues grown in the laboratory that mimic developing skin. Organoids have been grown to imitate various organs, including the gut, lung, kidney and brain[7]. Because organs consist of many cell types, organoids are typically formed from pluripotent stem cells, which have the ability to form all adult cell types. These can be embryonic stem cells or induced pluripotent stem cells, which are created by reprogramming adult cells to an embryonic-like state[8].

The epidermis and the dermis – the skin's other main component – are derived from different cell types in the early embryo. Lee *et al.* optimized the culture conditions needed to generate skin organoids containing both components from human pluripotent stem cells. The authors sequentially added growth factors to the stem cells. First, they used BMP4 and an inhibitor of the transcription factor TGF-β to induce formation of the epidermis. Next, they treated the cells with the growth factor FGF2 and an inhibitor of BMP, to induce the formation of cranial neural crest cells, which give rise to the dermis.

The cells grew in a sphere. After more than 70 days, follicles began to appear, which ultimately produced hair (Fig. 1). Most hairs were pigmented by melanocytes, which also develop from the cranial neural crest. Tissues associated with hair follicles – such as sebaceous glands, nerves and their receptors, muscles and fat – developed, too, leading to the formation of remarkably complete skin in a dish[9]. One missing component, however, was immune cells, which normally reside in and around hair follicles, and have diverse roles in the skin[10].

Lee and colleagues found that their organoids expressed genes that were characteristic of skin from the chin, cheek and ear. Interestingly, dermal cells on the scalp might also derive from the neural crest[11]. This suggests that the organoids might actually mimic scalp skin, and also highlights that it could be

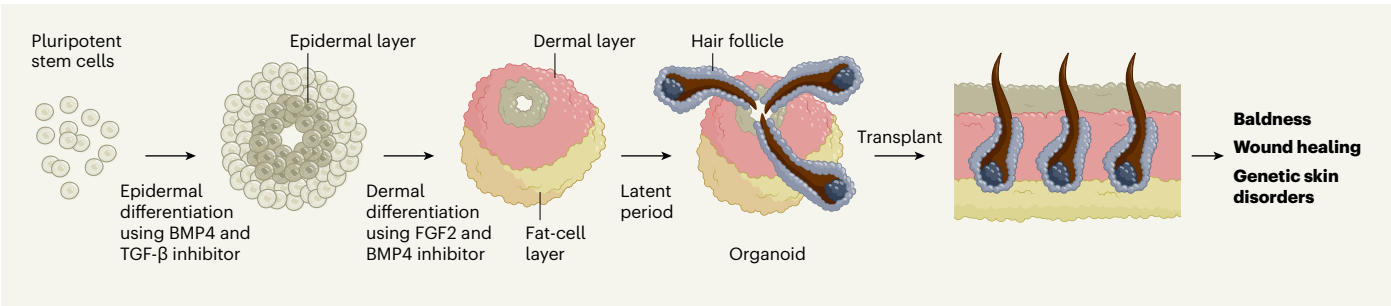

Figure 1 | Skin grown *in vitro* as a future clinical therapy. Lee *et al.*[2] grew human pluripotent stem cells (which can give rise to all cell types) into spherical skin-like structures called organoids *in vitro*. To achieve this, they treated the cells with growth factors (BMP4 and a TGF-β inhibitor) that promote growth of the skin's epidermal layer and then with other growth factors (FGF2 and a BMP4 inhibitor) that induce formation of the dermal layer (a fat-cell layer also forms at this stage). After a long latent period (more than 70 days), the full complement of skin cells formed in the organoid, including around 50 hair follicles. When the organoids are implanted into skin, the hair follicles naturally orient themselves in the correct direction. It is possible that these organoids could be used to treat baldness and genetic skin disorders, and to promote wound healing.

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possible to tailor the authors' protocol to generate skin that has the characteristics of different body sites, by altering the culture conditions in which the cells are grown.

The group's organoids will be a perfect tool for analysing the roles of various biological pathways in skin development — small-molecule inhibitors or inhibitory RNA molecules can be used to block proteins or pathways and to investigate the effects on skin growth. The organoids can be used in combination with genome-wide association studies or other genetic data to analyse how particular genetic mutations alter skin development. They can also help to model diseases of the skin and hair and to screen experimental drugs for any toxicities and for their efficacy.

Beyond these *in vitro* benefits, the authors demonstrated that the organoids have therapeutic potential *in vivo*. They transplanted the organoids onto immunodeficient mice (to ensure the graft was not rejected by the animals' immune system), and showed that just over half of organoids go on to form hair, which is distributed over the surface of the graft. This illustrates the exciting potential of introducing skin organoids into wounds to encourage healing and prevent scarring, or transplanting them into areas lacking hair.

However, several questions remain before this therapeutic approach becomes a reality. For instance, how efficiently and reproducibly do hairs develop? How many cells are needed to eventually form a hair follicle once grafted? Lee *et al.* began to answer the first of these questions by showing that a separate laboratory could grow hair in organoids using the same culture conditions. However, dealing with variability between individual stem cells and between the stem cells from different people are daunting challenges.

The prolonged length of time required for organoids to develop hair follicles mimics fetal skin development[12]. Similarly, in both settings, the skin undergoes a latent 'resting' phase before follicles begin to grow. This is a fascinating area for future study. However, it took 140 days before organoids were ready for engraftment, which could impede the therapeutic potential of the work — someone with burns, for instance, cannot wait that long for a skin graft. Further studies to understand the molecular events taking place during this latent phase should provide strategies for accelerating this process using molecules that alter relevant signalling pathways.

Several other aspects of the authors' approach will also need to be optimized before it can move to the clinic. The hairs that grew in the current study were small; in future, further optimization of culture conditions will be needed to form large scalp hairs. Better characterization of some components used in the culture cocktail — such as a protein mixture called Matrigel — will be necessary to ensure that they comply with good manufacturing practices. And future work might need to move away from using pluripotent stem cells, which can have undesirable side effects, such as promoting tumour formation. An appealing alternative might be to use adult stem cells.

Despite these caveats, Lee and colleagues' study is a major step towards a 'cure' for baldness in humans, and paves a way towards other, greater therapeutic possibilities. At a minimum, it is worth a shout-out on a late-night show. The work holds great promise of clinical translation — we are confident that research will eventually see this promise realized.

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Astrophysics

A fast radio burst with an unexpected repeat period

Bing Zhang

Observations of millisecond-long radio bursts from beyond the Milky Way have revealed a repeat pattern with a roughly 16-day period — a finding that adds to the enigma of the origin of these bursts. **See p.351**

Mysterious flashes of radio-frequency electromagnetic radiation, which last for just a few milliseconds, have baffled astrophysicists since their discovery[1] in 2007. Originating from outside the Milky Way[2], most of these fast radio bursts (FRBs) seem to be one-off events, but some sporadically emit repeated signals[3]. On page 351, the Canadian Hydrogen Intensity Mapping Experiment Fast Radio Burst (CHIME/FRB) Collaboration[4] reports the first FRB source that produces an intriguingly regular pattern of bursts, with a period of about 16 days.

The CHIME telescope has a large, instantaneous field of view (about 200 square degrees) that observes light in the 400–800-megahertz frequency range, which is ideal for searching for FRBs. One of the earliest repeating FRB sources discovered[5] by CHIME was FRB 180916.J0158+65. Because the source regularly falls into the telescope's field of view, it has been automatically monitored daily for an extended period of time. From 16 September 2018 to 4 February 2020, the telescope detected 38 bursts from the source. These bursts show a period of 16.35 ± 0.15 days. The window of activity during each period is about 5 days, with most bursts during this window concentrated into a time of roughly 0.6 days.

Establishing such a long periodicity for an astrophysical object is not easy, especially when only a few dozen events have been observed. One needs to carefully analyse the observational data to search for an active time window, a task that is complicated by the fact that the period of the putative regular bursts is unknown. False periods have been claimed before for other astronomical objects, such as quasars, because of overlooked red noise — random variations that can produce intervals of seemingly periodic behaviour[6].

The CHIME/FRB Collaboration carried out careful statistical analyses of its data, and claims that the chance of the periodicity arising from random flashes is only 1 in 10 million. There is a small possibility of 'aliasing' — the period might have been misidentified because the daily observation of the FRB source by the CHIME telescope was short. However, the authors argue that such aliasing is unlikely. Future independent confirmation of the periodicity using other telescopes would strengthen confidence in the authors' conclusion.

Let us accept that the reported period is real. Does this help us to identify the

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