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New hair from healing wounds

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Abstract

In mammals, most wounds heal by repair, not regeneration. It now seems that, as they heal, open skin wounds in adult mice form new hair follicles that follow similar developmental paths to those of embryos.

A person whose leg is amputated is left with a stump, whereas some amphibians have the awe-inspiring ability to regenerate new limbs after amputation. Overall, adult mammals have very limited regenerative ability; this could be due to a lack of stem cells or the absence of proper environmental signals. On page 316 of this issue, Ito *et al.*¹ report an unexpected finding that could change our current understanding of repair and regeneration in adult mammals. They show that the outermost skin layer — the epidermis — of wounded adult mice can regenerate new hair follicles during healing, and that this ability depends on the characteristics of the wound.

Observations some 50 years ago had indicated that, in mice, rabbits and humans^{2–5}, some hair follicles develop anew after wounding. But because of a lack of definitive evidence, these findings had generally been discounted. Now, using advanced cellular and molecular techniques to study normal adult mice, Ito *et al.* have rediscovered these forgotten phenomena. The authors made large wounds (1–2.25 cm²) on the animals' backs, to the full depth of the skin. They found that if, following wound closure, the healed wound was larger than around 0.5 cm in diameter, new hairs formed at the centre of the wound. An examination of the sections of the healed skin revealed changes that resembled various stages of embryonic hair-follicle development. The new hair follicles grew, passed through the hair cycle, and eventually became indistinguishable from neighbouring hair (Fig. 1).

Why has this phenomenon previously been missed? The reason might be that large wounds in humans are treated with sutures and dressings. Although such procedures help wound closure, they might not be ideal for the generation of new hair follicles. Similarly, it is not common practice to leave wounds open in mice. The authors did this here because they wanted to trace the fate of hair-follicle stem cells, which normally reside in the bulge in the hair follicle (Fig. 1), during wound healing. Thus, a combination of altered experimental design and careful observation led to these exciting findings, which verify the preliminary observations from the 1950s and help to explain the controversy.

What is the origin of the cells that make up these new hair follicles? Are they derived from existing hair follicles located at the wound edge, or from inter-follicular epidermis? Under normal conditions, the epidermis and the hair follicles maintain separate stem-cell compartments⁶⁻⁹. Following wounding, however, cells derived from the hair bulge contribute to reepithelialization — a process of new epidermis formation to cover the denuded dermis layer. This indicates that hair-bulge stem cells can turn into wound epidermis, although their contribution seems to be transient; with the exception of some cells from the upper part of the follicles, most of the hair-bulge-derived cells later disappear from the wounded epidermis⁶⁻⁹.

To determine the origin of the hair follicles that develop following wound repair, Ito *et al.*¹ used a mouse model in which the bulge cells or inter-follicular epidermal cells were genetically labelled before wounding, so that they could be traced afterwards. The authors found that cells constituting the newly formed hair follicles are derived from inter-follicular epidermis, and not from existing hair bulges. Whether the new hair follicles themselves are generated from epidermal stem cells or through de-differentiation of existing epidermal cells is unknown.

That the epidermis can turn into skin appendages (hairs, glands, feathers) is not entirely surprising. Previous studies have shown that, by combining cells from different tissue components under appropriate experimental conditions, scales can turn into feathers, oral mucosa (the membrane covering structures inside the mouth) can turn into tooth-like appendages, and even the corneal epithelium can become hair follicles¹⁰. Some of these changes can be achieved by altering the balance of relevant molecules in the cell. For example, β -catenin is a component of a signalling pathway mediated by Wnt proteins that is involved in regulating development. Increasing the activity of β -catenin can trigger the formation of new hair follicles in the interfollicular epidermis of adult mice without the use of hair-bulge stem cells¹¹. However, such cellular processes are occurring under experimental conditions. What is remarkable about the findings of Ito and colleagues is that skin wounds stimulate the formation of hair spontaneously, as part of the normal healing process.

Ito *et al.*¹ went on to show that wounding activates the Wnt-mediated signalling pathway, which is essential for normal hair development and cycling¹². Inhibiting this pathway in the skin during wounding led to a substantial decrease in the number of new hairs. By contrast, when mice with increased Wnt activity in their epidermal layer were wounded, there was a significant increase in new hair follicles compared with mice with normal Wnt activity. As these cellular events seem to recapitulate those seen in embryonic development, it is possible that hair formation during embryogenesis and following wounding share several signalling pathways, including Wnt.

What are the essential criteria for triggering the formation of new hair follicles in a patch of adult skin? The size of the healed wound seems to be critical. This implies that an 'embryonic skin-like field' must be established first. Selforganization of hair follicles then progresses, and periodically arranged primordia (aggregates of embryonic cells that indicate the first traces of a structure) emerge. As new hair patterns after wounding are not

predetermined, it is possible to manipulate the number and size of the follicles through positive- and negative feedback regulation of inhibitors and activators of signalling pathways such as Wnt^{10,13}.

Adult organisms contain several types of cells with remarkable regenerative potential^{12,14,15} — if we could only provide the appropriate chemical and physical environment. The best teacher for this is nature. Indeed, an event that parallels the work of Ito and colleagues is the regeneration of deer antlers. After an antler is cast, the large open wound that forms is followed by re-epithelialization and the development of new hair follicles, as well as budding of the new antler¹⁶. Further studies on animal models should reveal other unexpected and ingenious ways of awakening stem cells with appropriate environmental cues when regeneration is needed¹⁰.

Repair and regeneration seem to be competing processes. As closing wounds fast is essential for survival, repair often dominates. Regenerative medicine promises to identify natural healing power and a shift from repair to regeneration. Thus, by simply altering the environment of stem cells¹⁰ during wound healing, future wounds might heal with appendages reformed. As human and mouse skin heals differently, the results of Ito *et al.*¹ are yet to be verified in humans. However, these findings will undoubtedly inspire new thinking in the management of alopecia, in tissue engineering and in the regeneration of other organs.

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Figure 1. Formation of new hair in a healed wound

a, Ito and colleagues¹ found that when a large open wound is generated in the skin of adult mice, re-epithelialization occurs. **b**, If the healed skin is larger than around 0.5 cm in diameter, new hair follicles originating from the epidermis form in the centre of the wound.