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Hair Cycling and Wound Healing: To Pluck or Not to Pluck?

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The incidence of nonhealing wounds (diabetic foot, pressure, venous, and arterial ulcers) is reaching epidemic proportions, underscoring the need for new treatment modalities. Understanding hair follicle biology and its potential to accelerate wound healing may offer new treatment strategies. In this issue, Ansell *et al*. show that wounds on anagen skin heal faster than those on telogen skin, suggesting that hair cycle stages may influence healing outcome.

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The clinical need to improve and accelerate wound healing is tremendous because the incidence of chronic ulcers (venous, diabetic foot, and pressure) is rising to epidemic proportions. Annually, more than 4 million Americans are hospitalized with a deep soft-tissue infection of the skin, and over $25 billion dollars are spent on wound care. The true cost, however, is the mortality and morbidity associated with nonhealing wounds, which disproportionately affect elderly, disabled, and immobile patients as well as those with vascular disease and/or diabetes (Lebrun *et al.*, 2010).

Ultimately, the goal of wound healing experts is to integrate the knowledge gained from studies of wound healing and hair follicle biology toward regenerative pathways (rather than repair). Recent reports of *de novo* folliculogenesis in full thickness wounds of adult mice underscored the potential use of hair follicle biology for tissue regeneration. In this issue, Ansell *et al.* (2011) utilized the C57BL/6 mouse model and two types of wounding (incisional and excisional full thickness) to study the influence of the hair cycle on wound healing.

Clinicians have long reported that hair-bearing areas tend to heal more rapidly than those lacking hair follicles. Conversely, laboratory investigators have shown that hair follicle stem cells contribute to the wound healing process significantly, although under normal conditions they do not participate in epithelial homeostasis (Ito and Cotsarelis, 2008). Upon wounding, epithelial stem cells residing in the hair follicle migrate to the epidermis to aid re-epithelialization (Ito *et al.*, 2005).

Acute wound healing is a multifaceted process involving numerous resident skin cells as well as circulating cells. The process is orchestrated by tightly regulated cross-talk among wounded cells, cells in the vicinity of a wound, and cells that migrate from a distance to a wound site after injury. These cells include keratinocytes, fibroblasts, platelets, macrophages, and endothelial cells as well as local progenitors (residing in basal epidermis and hair follicles) and circulating progenitors (bone-marrow derived) (Barrientos *et al.*, 2008), resulting in inflammatory response, matrix deposition, cellular migration, and proliferation. The hair follicle serves not only as a source of progenitors but also as an anchor and chemoattractant to other progenitor cells.

The hair follicle is a mini-organ formed during embryonic development by epithelial–mesenchymal interactions; it is composed of multiple lineages of epithelial cells that include the hair matrix, hair shaft (medulla, cortex, and cuticle), and inner and outer root sheaths, as well as dermal components that include the dermal papilla and the dermal sheath (Paus *et al.*, 1999). Once formed, the epithelial components of the hair follicle are renewed through cyclical phases of anagen, catagen, telogen, and exogen (Muller-Rover *et al.*, 2001). Anagen marks the hair growth phase, in which keratinocytes of the hair matrix within the lower bulb region of the hair follicle proliferate rapidly and produce the hair shaft. During catagen, hair follicle proliferation ceases, and the lower part of the follicle regresses through cellular apoptosis. Telogen is the resting stage of the follicle, during which the hair shaft is maintained in the absence of proliferation. Following telogen, the

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Clinical Implications

- Inducing the anagen phase of the hair cycle (such as by hair plucking) prior to wounding may accelerate wound closure.
- Future studies will characterize the contributions of cells in each phase of the hair cycle to wound healing.

hair follicle enters the exogen phase, during which the hair shaft falls off. Hair follicle stem cells responsible for cyclical renewal of hair follicles reside in an area of the hair follicle called the bulge, which is located in the outer root sheath below the sebaceous gland (Cotsarelis *et al.*, 1990). Both the bulge and the dermal papilla are conserved throughout the cycle of the hair follicle, and they interact to give rise to the components of the growing follicle.

Beside its primary function of regenerating the hair shaft through periodic cycling, the hair follicle also contributes cells to the epidermis during wound healing. This function has long been known by clinicians, who have observed that the denuded skin of burn patients heals through the apparent repopulation by epidermal cells originating from intact hair follicles in the dermis. In addition, Argyris (1976), who examined tissue sections of mouse skin after epidermal ablation, noted the presence of "epithelial islands" contiguous with underlying hair follicles in the initial stage of re-epithelialization, suggesting the now well-appreciated function of the hair follicle as a reservoir of epithelial cells for regenerating interfollicular epidermis.

These pioneering observations led to subsequent studies that identified the bulge as an origin of the epithelial stem cells utilized for regenerating the interfollicular epidermis in response to wounding (Ito *et al.*, 2005). Importantly, recent studies discovered other populations of epithelial stem cells within distinct regions of the hair follicle (Snippert *et al.*, 2010) that also give rise to skin epithelial cells under specific physiological conditions, leading to further appreciation of the hair follicle's physiological significance in wound healing. Yet, surprisingly, the field lacked research into the influence of the hair follicles on wound healing.

Ansell *et al.* (2011) characterized the response to wound healing in the skin of mice whose hair follicles were in the anagen and telogen phases. Wounds on anagen skin healed faster than those on telogen skin (Figure 1). In anagen skin accompanied by interfollicular epithelial cells, the cells of the outer root sheath proliferated faster at the onset of re-epithelialization; the authors describe this as one of the mechanisms by which the increased rate of re-epithelialization is achieved. This rate decreased later in the healing process. In telogen skin, however, increased proliferation of both the follicular and the interfollicular epithelial cells occurred later. This delay in proliferation could be a compensatory phenomenon in what could be viewed as "catch-up healing" that allows telogen skin to achieve complete re-epithelialization. Whether it occurs at the same time as in anagen skin requires further elucidation. Given the significant contribution of follicular epithelial stem cells to re-epithelialization, the distinct proliferation patterns of anagen and telogen skin provoke important questions. For instance, is epithelial stem cell constitution conserved among the hair cycle phases? How differently within these phases do these populations communicate and contribute cells to append wound healing? Addressing these questions will be significant not only for controlling hair growth activity but also for creating strategies to accelerate wound healing.

In addition to accelerated re-epithelialization, the authors found increased vascularization and significantly reduced skin inflammation in anagen skin wounds, characteristics that may be relevant in efficient wound healing. It is known that improved follicle vascularization promotes hair growth and the anagen phase is associated with increased angiogenesis (Mecklenburg *et al.*, 2000). Given that wound healing is a tightly regulated process, it is not surprising that excess inflammatory cells and granulation tissue in telogen wounds lead to delayed wound healing. Furthermore, it is important to note that wound reduction in anagen skin is detected as soon as 5 hours after wounding, much earlier than the onset of increased epithelial cell proliferation. This suggests that initial wound contraction in anagen skin also contributes to accelerated wound healing. Interestingly, Ansell *et al.* (2011) found no significant differences in myofibroblast marker localization between anagen and telogen wounds.

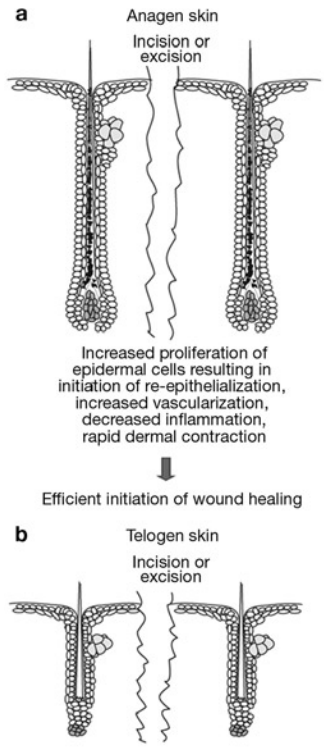

Figure 1. Wounds made on anagen-phase skin heal faster than those on telogen skin. The scheme depicts wounded skin with the hair follicle in the anagen (**a**) and telogen (**b**) phases of the hair cycle. Incisional or excisional wounds made on anagen-phase skin show increased skin periwound hair follicle outer root sheath and interfollicular epidermal proliferation, decreased inflammation, and increased angiogenesis, accelerating the wound healing process.

Both anagen and wound healing are associated with cell proliferation and migration, angiogenesis, and extracellular matrix remodeling. Microarray analysis further confirmed this overlap and identified the same signaling pathways to be involved in wound repair and the anagen phase of hair cycling (Ansell *et al*., 2011).

In summary, hair follicles are perceived by many as essential for the structural integrity of skin, promoting maintenance and regeneration of this organ. The report by Ansell *et al*. (2011) highlights the nexus between hair follicle biology and wound healing and raises awareness of the potential for studies in animal models of wound healing to be influenced by hair cycle stage. If the authors' data are confirmed in human studies, their findings may ultimately have clinical implications. It is conceivable that wound healing may be accelerated in patients by manipulating hair follicle cycling prior to or during wound healing. For instance, hair plucking could be performed prior to surgery to induce anagen hair cycling and speed surgical wound healing.

Currently, the field of chronic wounds is driven by the critical clinical need to achieve closure and tissue restoration. By understanding the mechanisms that regulate neogenesis and hair cycling, one can envision future therapies in which the paradigm of tissue repair and restoration is shifted toward regenerative pathways.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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