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Viewpoint

Reflections on how wound healing-promoting effects of the hair follicle can be translated into clinical practice

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Abstract: Clinicians have long reported that hair-bearing areas tend to heal more rapidly than those lacking hair follicles. In the past decade, numerous scientific studies have corroborated clinical evidence, showing a direct nexus between the human hair follicle and the wound healing process. The migration of epithelial follicular stem cells to the skin surface to help in the wound re-epithelialization and the effect of the hair cycle on the wound healing rate underline the influence of the hair follicle in the healing process. In clinical practice, non-healing wounds are pathologies of high prevalence with significant associated burden costs for the healthcare system. As the population ages, the prevalence of this pathology is expected to increase in future years. The recent advances in understanding the biology of hair follicle stem cells have created the challenges of using this newly acquired knowledge in practical therapeutic applications. Chronic leg ulcers are an example of the targeted pathologies that urgently need better therapies. In this essay, our aim is to raise interest in this question, reviewing what is known in relation to the connections between hair follicles and wound healing, and elaborating on future directions that the field might take, including implications for clinical practice.

Key words: chronic leg ulcers – hair follicle – hair grafting – human skin – wound healing

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Introduction

Skin wounds heal through a complex process in which several consecutive, partially overlapping phases may be recognized (1). Stem cells of both the epidermal (2) and dermal (3–5) compartments of skin, as well as their interactions with remodelling components of the dermal extracellular matrix (6,7) and tissue morphogens (8,9), all seem to play an important role in skin wound repair and may also be relevant in associated pathophysiological conditions such as certain types of skin cancer (10,11).

The hair follicle is a well-known reservoir of several types of skin stem cells (12–14) and these seem to be implicated in many aspects of wound healing (15) including unexpected ones such as an increased protection of the wounded skin against ultraviolet light-mediated damage (16,17). Although most of the current mechanistic insight comes from experiments performed on model organisms, the field is now reaching maturity, with clinical applications beginning to take place which are expected to increase in the near future. Thus, the following sections will elaborate on what is known in relation to the connections between hair follicles, endogenous stem cells and cutaneous wound healing (18–20), as well as reflect on future directions the field might take and their implications for clinical practice.

The Hair Follicle and its central role in the wound healing process

The clinical evidence

There is abundant clinical information to support the argument that wound healing starts around the hair follicles. A paper published in 1945 by Bishop (21), a neuroanatomist from Washington University in St. Louis, remains the most enlightening paper about the clinical evolution of the wound healing process *in vivo* in humans. Dr. Bishop studied how the connective tissue and epithelium regenerate after removal of horizontal layers of the skin. Moreover, he performed his experiments in the hardest and most objective way possible by self-inflicting cutaneous wounds on his forearm at different tissue depths and observing the healing process that took place clinically and histologically. His observations, which have generally not been given the recognition they deserve in the literature, remain completely valid and consider the hair follicle to be the principal cutaneous structure whose presence or absence conditions the outcome of the healing response. He reported that (i) re-epithelialization starts around the remaining hair follicles and from the marginal epithelium; (ii) when only the papillary layer is removed coarse mounds of granulation tissue develop at the sites of follicles; (iii) when the skin is destroyed down to the deep dermis, the granulation tissue that regenerates comes from the connective tissue surrounding the hair follicles and (iv) scar formation occurs when removal is sufficiently deep to destroy the bases of hair follicles.

One demonstration of the pivotal role of the hair follicle in wound healing is the fact that wounds in high hair density areas (e.g. scalp wounds) heals faster than those in non-hairy areas (e.g. wounds on palms). This property has been clinically demonstrated when scalp is the donor source for harvesting split-thickness grafts: the healing time to complete re-epithelialization of the donor wound averages 5–6 days against 10–14 days in areas such as the thighs, buttocks or abdomen (22–25).

Basic science supporting the role of the Hair Follicle as wound healing inducer

Hair follicles and other skin appendages might have a wound healing-promoting role by acting simply as hubs from where re-innervation (26) and capillary sprouting (27,28) of wound beds proceed. Notwithstanding these (possibly key) roles, a major capability of the hair follicle seems to be the outsourcing of precursor cells for immediate local skin repair (29,30). Accordingly, Langton et al. (31) reported how, in the absence of murine tail skin hair follicles, cutaneous wounds heal with a significant delay in re-epithelialization. Furthermore, it is not only the presence of hairs that accelerates wound healing; the stage of the hair cycle also appears to be important. In this respect, Ansell et al. (19) showed that wounds heal faster when made on skin with hair follicles in anagen phase as opposed to telogen phase. The hormone Leptin, which has long been known for its role in wound healing (32), was recently shown to be secreted by dermal papilla cells in connection with anagen induction (33,34). Interestingly, *mTORC1* activation in bulge stem cells may modulate the timing of anagen initiation in hair follicles (35) and this might have implications on wound healing through related pathway effectors *Pten* (36) and *Stat3* (37). In recent years, it has been observed that, at least in the laboratory mouse, hair follicles cycle in a coordinated manner within macroscopic 'hair domains'. The availability of mouse strains that permit follow-up of hair follicle dynamics *in vivo* (38) will likely impact upon our knowledge of the wound healing/HF neogenesis process, although clinical translation of these findings remains uncertain due to major differences between human and mouse hair follicle biology (13).

At the cellular level, it seems clear that upon wounding bulge epithelial follicular stem cells migrate to the epidermis to aid with the rapid re-epithelialization of wounded skin (29,39–41). Perifollicular mesenchymal cells from the dermal sheath and/or dermal papillae also appear to participate in the wound healing response, moving out of the follicles into the wounds, where they contribute to dermal fibroblasts and myofibroblasts (42–44).

Along with the seminal findings by Ito et al. (45) on wound-induced hair follicle neogenesis in mice, which showed that skin cells in a position central to the wound bed presented the ability to dedifferentiate (reprogramme) themselves into hair-inducing cells, it has been proposed that the repair and regeneration programmes might be mutually exclusive, with the wound borders preferentially promoting repair over regeneration in the short term (46). Prostaglandin signalling seems to be involved in this process (47) although wound-induced HF neogenesis is dependent on the mouse strain used. Further basic research is required to improve current mechanistic understanding in this respect (48). In contrast to mice, humans lack the ability for hair follicle regeneration after wounding, which has been explained by the relative lack of a robust population of $\gamma\delta$ T cells in the dermis compared with mice. Fgf9 secretion by the $\gamma\delta$ T cells seems to be the key factor that induces hair follicle neogenesis after wounding (49).

Could we take advantage of hair follicles as a therapeutic tool to stimulate healing of cutaneous wounds?

Given the abundant body of evidence indicating the active role of the HF in wound healing, it is surprising that there are so few reports about the use of this follicular machinery as a therapeutic weapon in clinical practice to stimulate wound healing. Most of these reports that do exist refer to clinical cases of burns or surgical defect wounds treated with artificial dermis coverage followed by hair follicle grafting (50–52).

One of the wound pathologies that urgently need better and less costly therapies is the chronic leg ulcer (CLU). CLUs mostly affect the lower part of the leg and are caused by venous insufficiency, followed by arterial insufficiency and neuropathy (especially of diabetic aetiology). It is estimated that one in every 100 adults will suffer from venous CLU at some point in their lifetime (53). Besides the high prevalence, CLUs are one of the most costly diseases for health services worldwide; accurate estimations of the cost give a figure of 9569 Euros per ulcer per year (54).

Compression therapy (to treat the oedema and venous insufficiency) and wound dressings (to protect the wound bed from trauma and absorb exudate) continue to be the mainstay treatment for venous CLU in clinical practice (53). However, some 20% of ulcers remain unhealed. For these difficult-to-heal venous leg ulcers, additional treatments such as drug therapy (pentoxifylline, aspirin, granulocyte macrophage-colony stimulating factor) or skin grafting to promote healing have been used (55). These include autografts taken directly from the patient (pinch grafts, split-thickness grafts, full-thickness punch grafts) or after growing the patient's cells to form a thin film in the lab (cultured keratinocyte autografts); allografts applied as a sheet of bioengineered skin grown from donor cells (allografts) (56–59); and a promising new cell therapy (60,61) using a spray formulation composed of neonatal allogeneic fibroblasts and keratinocytes. The use of tissue-engineered products and non-hair follicle stem cells for cell-based therapies for cutaneous wounds lies outside of the scope of this review [see recent review articles (62–64)].

In spite of this diversity in therapies, experts in wound healing commonly agree that in most cases, there is insufficient evidence as to their actual effectiveness, and they argue that there is a need for more and better quality trials (53,57,65).

Hair-related therapies for chronic leg ulcers

Plucking hairs from a patient's scalp to obtain epidermal autografts that could be transplanted to the wound bed was the first original hair-related and commercially available therapy for CLUs (EpiDex®; EuroDermBiotec& Aesthetics, Stuttgart, Germany). This method involves isolating keratinocytes from the external root sheath of the plucked hairs and culturing them *in vitro* to obtain epidermal sheets that will be transplanted to the wound bed of the ulcer. Depending on wound size, 70–350 anagen scalp hairs are plucked (66). A multicentre, randomized study has shown that this hair-derived epidermal equivalent is as effective as split-thickness skin autografting in healing recalcitrant vascular leg ulcers (67), especially chronic venous leg ulcers of small and medium size (68,69). The practical advantages of this therapy are its non-invasive nature and easy handling in an outpatient setting with no need for anaesthesia or donor site surgical intervention. Disadvantages include the time required for processing the epidermal sheets: the lab work requires approximately one week to obtain a primary keratinocyte culture and another 2 weeks to grow the organotypic epidermal discs for grafting.

As CLUs are devoid of hair follicles, the epidermis can regrow only via cells migrating from the edges of intact skin. A more pragmatic approach of hair-related therapy for CLU would be to directly insert in the wound bed terminal anagen hair follicles (har-

vested from the patient) containing epithelial and mesenchymal stem cells that when implanted within damaged tissue would eventually proliferate, migrate away from the implant and induce healing of the ulcer. The technical procedure can be easily reproduced and is identical to the so-called follicular unit extraction (FUE), a minimally invasive surgical procedure commonly used in hair transplantation for androgenetic alopecia (70). A circular punch of 1 to 2 mm in diameter is used to remove the hair grafts under local anaesthesia (71). The small holes left in the donor scalp heal rapidly in 4–5 days by second intention, leaving clinically undetectable pinpoint scars. It should be noted that the use of punch grafting in CLUs is not new (72–74), however, the difference with this approach is that instead of harvesting punch grafts from the thighs or buttocks which are preferentially composed of epidermal and dermal tissue with very sparse terminal hair follicles, the grafts are harvested from the patient's scalp, containing mainly hair follicles. As a consequence, a much larger amount of stem cells (both bulge epithelial stem cells and mesenchymal stem cells) is delivered to the wound bed if the graft punches are harvested from the scalp as opposed to the classical less-hairy donor areas. A pilot study of scalp hair grafting in CLU (71) demonstrated the positive effect of the hair grafts in stimulating wound healing of leg ulcers of long duration (Fig. 1). At the 18-week endpoint, a 27% ulcer area reduction in the experimental square was observed against 6.5% in the control square. Improvement of clinical symptoms (appearance of granulation tissue, wound border reactivation and a lesser amount of exudation) was noted in 7 of 10 cases. Further trials with higher sample sizes need to be performed to confirm these promising results as well as to compare the differences in the healing outcome of punch grafts harvested from the scalp versus punch grafts harvested from hair-poor areas.

It is interesting to note that patient age should not be a drawback for using hair follicles in chronic wounds of elderly patients. It has been shown that ageing does not significantly alter the density of bulge hair follicle stem cells nor the expression of eHFSC marker proteins and bulge cell dsDNA content per hair follicle (75). In contrast, extrafollicular modulators such as follistatin diminish with age (76). The reasons for the observed delay in healing of elderly patient wounds are multiple and possibly unrelated to chronic non-healing wounds, which are associated with comorbidities of greater prevalence in old age (77–79).

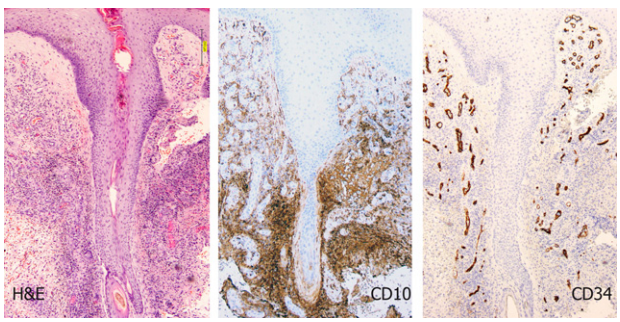

Figure 1. Histological sections of hair follicle transplants into CLUs. Left image shows an H&E section of a hair follicle transplanted into the wound bed of a chronic leg ulcer. Granulation tissue is seen surrounding the transplanted hair follicle. The centre image shows strong CD10 immunoreactivity, which reflects an increased number of perifollicular/dermal sheath mesenchymal cells. The image on the right shows CD34 immunostaining of the same histological section, delineating the increased vascularity (neovascularization) surrounding the hair follicle graft.

Future challenges

In conclusion, what we already knew from the clinical experiments of Bishop (21), namely that the hair follicle plays a key role in the initial wound healing response, can now be explained at cellular level in the light of recent advances in hair stem cell biology. The challenge today, however, is to pursue imaginative strategies on how to use and apply this knowledge in specific clinical situations which deal with difficult-to-heal or chronic cutaneous ulcers.

By way of example, a recent study describes the use of a hydrogel formulation composed of LGR6+ follicular stem cells that appears to enhance the wound healing and angiogenic response when transplanted into full-thickness skin wounds in mice (28). Another different strategy would be to incorporate epithelial and dermal papilla cells with follicle neoformation capacity into composite grafts, which would then incorporate hair follicles or hair follicular cells into the wound bed, inducing the healing response (80,81). Moreover, the capability of generating large numbers of human epithelial HF stem cells from induced pluripotent stem (iPS) cells (capable of generating all hair follicle lineages) (82) is now possible representing a new possibility for the development of wound healing cell therapies that could be applied on the wound bed of non-healing ulcers, for example in the form of a cell spray (83).

Importantly, the use of expanded cells in the clinic entails major financial and regulatory challenges (84) and thus a lot of cell therapy activity has focused so far on minimally manipulated and insufficiently characterized cell populations (85). It is therefore imperative that technical and regulatory advances make these approaches feasible in the clinical practice (86).

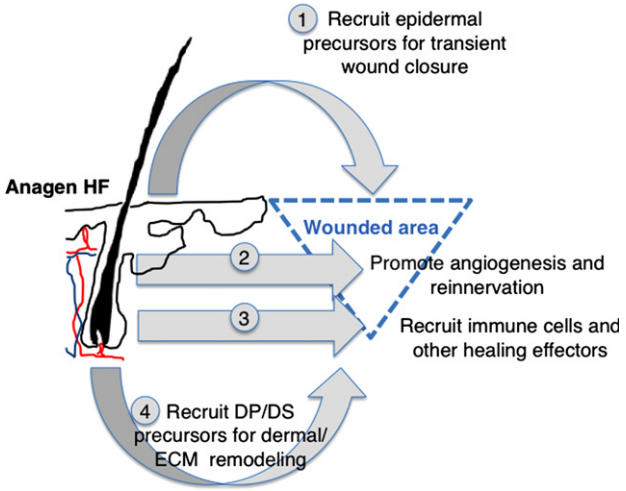

Figure 2. Proposed mechanisms on the effect of the hair follicle as a healing promoter on chronic cutaneous wounds. (1) Hair follicle-derived epidermal stem/precursor cells are recruited immediately after wounding for transient closure, newly formed epidermis being later replaced by new layers generated from interfollicular epidermal precursors. (2) Hair follicles, as other epidermal annexes, are highly vascularized and innervated (red and blue lines in the figure). It seems plausible that paracrine signals and cell precursors derived from the hair follicle promote angiogenesis and re-innervation of the wounded area. (3) The perifollicular area is also a reservoir for mast cells and macrophages and these cells might have a capital role in recruiting immune cells and possibly mesenchymal stromal cells through immunomodulatory cytokine secretion. (4) Mesenchymal precursors resident at the dermal papilla or dermal sheath might also be recruited at later stages of wound healing for dermal and extracellular matrix (ECM) remodelling.

Alternatively, the promotion of endogenous regeneration capabilities seems to be a more realistic approach, once the key factors and cell types responsible for it have been properly delineated. For instance, it is suspected that substances that accelerate hair growth, for example TRH, may also promote wound healing (87). This is an area that needs to be explored using animal and human wound healing models (88–90).

In conclusion, the connections between hair follicle biology and wound repair seem to be multiple and extremely relevant (Fig. 2). Carefully delineated experimental approaches are needed to further understand the key cell types responsible for endogenous tissue repair and the signalling pathways/factors that impact upon them. With such information at hand, future cell or small molecule therapy-based approaches for CLUs will be based on better rationales and thus benefit from improved design and outcome measurements.

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Author contributions

Jiménez, Poblet and Izeta take full responsibility of the contents of the manuscript. Jiménez and Izeta wrote the paper. Poblet provided Fig. 1 and Izeta provided Fig. 2. Critical revision of the manuscript for important intellectual content: Jiménez, Poblet and Izeta. Administrative support: Jiménez.

Conflict of interest

The authors have declared no conflicting interests.

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