Metadata of the chapter that will be visualized in SpringerLink

Book Title	Hair Follicle Regeneration
Series Title	
Chapter Title	Hair Follicles in Wound Healing and Skin Remodelling
Copyright Year	2022
Copyright HolderName	The Author(s), under exclusive license to Springer Nature Switzerland AG

Author		
	Family Name	**Plotczyk**
	Particle	
	Given Name	**Magdalena**
	Prefix	
	Suffix	
	Role	
	Division	Department of Bioengineering
	Organization	Imperial College London
	Address	London, UK
	Email	

Corresponding Author		
	Family Name	**Jimenez**
	Particle	
	Given Name	**Francisco**
	Prefix	
	Suffix	
	Role	
	Division	
	Organization	Mediteknia Dermatology and Hair Transplant Clinic, University Fernando Pessoa Canarias
	Address	Gran Canaria, Spain
	Email	fjimenez@mediteknia.com

Abstract	*Introduction*: Besides the primary role of hair follicles in producing hair shafts, these mini-organs have been shown to contribute to the healing and remodelling of the skin in the response to injury. There is an increasing number of clinical and experimental studies exploring the mechanisms by which hair follicles contribute to skin recovery. Mouse tracing experiments demonstrated that after skin injury, epithelial stem cells migrate out of the follicle to support wound re-epithelialization, while the mesenchymal cells from the hair follicle are mobilised to migrate into the wound bed and contribute to the repair of the dermis. Accordingly, there is a significant delay in wound healing in the absence of hair follicles, observed both in experimental studies in mice and in humans during clinical practice. In the healthy state, hair follicles induce changes to the surrounding skin, which occur in synchrony with the hair follicle cycle. Besides supporting wound healing and healthy skin remodelling, it remains to be investigated whether hair follicles could also remodel the fibrotic tissue formed after skin injuries. *Methods*: For the selection of literature covered in this chapter, we used Pubmed database with the keywords hair follicles in wound healing and skin remodeling, and hair follicles transplantation and wound healing. Publications related to the clinical use of hair follicle grafts for healing chronic cutaneous wounds are also discussed. *Results*: A large body of evidence supports the role of hair follicles in wound healing and skin remodeling. As demonstrated in several clinical studies, transplantation of autologous hair follicle grafts into chronic ulcers and difficult to heal wounds accelerate the healing of wounds. *Conclusions*: There is a great potential in exploring the role of hair follicles in wound healing and skin regeneration. Once we understand the exact mechanism by which hair follicles contribute to skin recovery, we can try to mimic this effect with therapeutic solutions.

A potential approach involves deciphering the populations of hair follicle cells that contribute to the observed effect and injecting them directly into wounds or scar tissue to improve the clinical outcomes. Alternatively, elucidating the paracrine effect of transplanted follicles would open up new avenues for therapeutic discovery, to replicate the combination of required factors that facilitate healing or scar remodelling.

Chapter 14
Hair Follicles in Wound Healing and Skin Remodelling

Magdalena Plotczyk and Francisco Jimenez

1 **Abstract** *Introduction*: Besides the primary role of hair follicles in producing hair
2 shafts, these mini-organs have been shown to contribute to the healing and remod-
3 elling of the skin in the response to injury. There is an increasing number of clinical
4 and experimental studies exploring the mechanisms by which hair follicles contribute
5 to skin recovery. Mouse tracing experiments demonstrated that after skin injury,
6 epithelial stem cells migrate out of the follicle to support wound re-epithelialization,
7 while the mesenchymal cells from the hair follicle are mobilised to migrate into the
8 wound bed and contribute to the repair of the dermis. Accordingly, there is a signifi-
9 cant delay in wound healing in the absence of hair follicles, observed both in exper-
10 imental studies in mice and in humans during clinical practice. In the healthy state,
11 hair follicles induce changes to the surrounding skin, which occur in synchrony with
12 the hair follicle cycle. Besides supporting wound healing and healthy skin remod-
13 elling, it remains to be investigated whether hair follicles could also remodel the
14 fibrotic tissue formed after skin injuries. *Methods*: For the selection of literature
15 covered in this chapter, we used Pubmed database with the keywords hair follicles
16 in wound healing and skin remodeling, and hair follicles transplantation and wound
17 healing. Publications related to the clinical use of hair follicle grafts for healing
18 chronic cutaneous wounds are also discussed. *Results*: A large body of evidence
19 supports the role of hair follicles in wound healing and skin remodeling. As demon-
20 strated in several clinical studies, transplantation of autologous hair follicle grafts
21 into chronic ulcers and difficult to heal wounds accelerate the healing of wounds.
22 *Conclusions*: There is a great potential in exploring the role of hair follicles in wound
23 healing and skin regeneration. Once we understand the exact mechanism by which
24 hair follicles contribute to skin recovery, we can try to mimic this effect with thera-
25 peutic solutions. A potential approach involves deciphering the populations of hair
26 follicle cells that contribute to the observed effect and injecting them directly into
27 wounds or scar tissue to improve the clinical outcomes. Alternatively, elucidating the

M. Plotczyk
Department of Bioengineering, Imperial College London, London, UK

F. Jimenez (✉)
Mediteknia Dermatology and Hair Transplant Clinic, University Fernando Pessoa Canarias, Gran
Canaria, Spain
e-mail: fjimenez@mediteknia.com

1

28 paracrine effect of transplanted follicles would open up new avenues for therapeutic
29 discovery, to replicate the combination of required factors that facilitate healing or
30 scar remodelling.

31 **Keywords** Hair follicles · Wound healing · Skin remodelling · Hair follicle cycle ·
32 Autologous hair transplantation

Key Points

34 • Hair follicles in the skin play an important role in stimulating healing. Hair follicle
35   epithelial stem cells migrate and are known to contribute to re-epithelialization,
36   while dermal remodeling is postulated to be regulated by the hair follicle dermal
37   sheath.
38 • Clinical studies using hair follicles transplanted into wounds have been performed
39   with successful outcomes in chronic ulcers and difficult-to-heal wounds and this
40   type of intervention seems to be a promising novel therapeutic tool.
41 • Hair follicles induce changes in healthy skin during hair follicle cycles (skin
42   remodeling). Their role in skin remodeling after injuries needs to be investigated
43   and translated to clinical practice.

Summary

45 The role of hair follicles in human skin is not to simply produce hair shafts but
46 to participate in many other functions including skin homeostasis and the wound
47 healing response to cutaneous injuries.
48   In this chapter, we will first explore the role that human hair follicles play in
49 wound healing and the clinical and experimental evidence that supports this connec-
50 tion. Then, we will summarize the latest translational clinical work that has been
51 performed using autologous hair follicle grafts (hair transplantation) as a therapeutic
52 tool to stimulate wound healing and discuss possible mechanisms through which hair
53 transplantation stimulates the healing response. Finally, we will comment on the role
54 of hair follicles in the remodeling of normal skin and fibrotic/scar tissue.

Hair Follicles and Wound Healing: Historical Studies

56 The first clinical studies suggesting an active role of hair follicles in the wound
57 healing response date back to the work of Brown and McDowell in 1942 [1]. In their
58 article, they suggest that during wound repair cells from the hair follicles dediffer-
59 entiate to cells that contribute to the healing of the wound. However, without doubt
60 the most enlightening and convincing paper demonstrating that hair follicles are key
61 contributors to the wound healing response after skin injuries in humans was written
62 by Bishop, a neuroanatomist from Washington University in St. Louis [2]. In this
63 paper, published in 1945, Bishop performed his experiments in the most objective

way possible by self-inflicting cutaneous wounds on his own forearm at different depths and observing the clinical and histological healing process. Bishop demonstrated that the remaining hair follicles left in the wound bed played a pivotal role in wound healing and that their presence or absence influenced the outcome of the healing response. More specifically, he concluded that: (1) re-epithelialization of the wound starts not only from the marginal epithelium but also from the remaining hair follicles; (2) scar formation occurs when the wound is sufficiently deep to destroy the bases of hair follicles; and (3) when the skin is destroyed down to the reticular layer, the granulation tissue regenerates most readily from the connective tissue surrounding the hair follicles. This granulation tissue is necessary for migration of the epithelial cells and subsequent healing of the wound surface.

This pioneering work of Bishop supports the well-known observation of clinicians nowadays that a wound made in areas of high hair density (and with terminal hair follicles) heals faster than a wound of the same size in a less hairy area. For example, the healing time of a 0.2–0.3 mm depth wound made on the scalp averages 5–6 days against the 10–14 days that it takes to re-epithelialize a wound of the same size made on the thighs, buttocks or abdomen [3]. This faster healing time is the reason why the scalp seems to be a very efficient area to harvest split thickness skin grafts for burn wounds [4].

The contribution of hair follicles in wound healing described by Bishop were later confirmed by Ito et al. who showed that follicular stem cells played a key role in re-epithelialization of the wounded epithelium, as will be discussed later in more detail [5].

Hair Follicles as a Therapeutic Tool to Stimulate Wound Healing: Clinical Evidence

In view of this ability of hair follicles to promote wound healing, several clinical studies have been successfully undertaken to demonstrate the use of autologous hair follicle grafts harvested from the scalp in stimulating the healing of chronic ulcers or other difficult-to-heal wounds [6].

The first clinical cases showing that hair follicles could be used as a therapeutic tool to stimulate wound healing were reported in the plastic surgery literature. These reports described a few patients with deep and extensive burns successfully treated with a combination of an artificial dermis that provided an immediate coverage of the wound, followed by autologous hair follicle grafting that accelerated healing and re-epithelialization [7–9].

The methodology used for implantation of hair follicles in non-healing wounds is basically the same as is used in hair transplantation techniques for the treatment of baldness, where hair follicles are harvested from the patient's occipital scalp (donor area) and inserted into the skin of the balding area (recipient area) (Fig. 14.1). These autologous transplanted follicles (also called hair grafts or follicular unit grafts) have

Fig. 14.1 The process of hair transplantation into wounds. In the upper image, hair follicles harvested from the donor site (scalp) are inserted with fine tip forceps into slits created in the wound bed. The lower image represents follicular epithelial and mesenchymal cells proliferating and migrating out of the hair follicle into the interfollicular skin, increasing vascularization and re-epithelialization, and supporting the healing of wounds
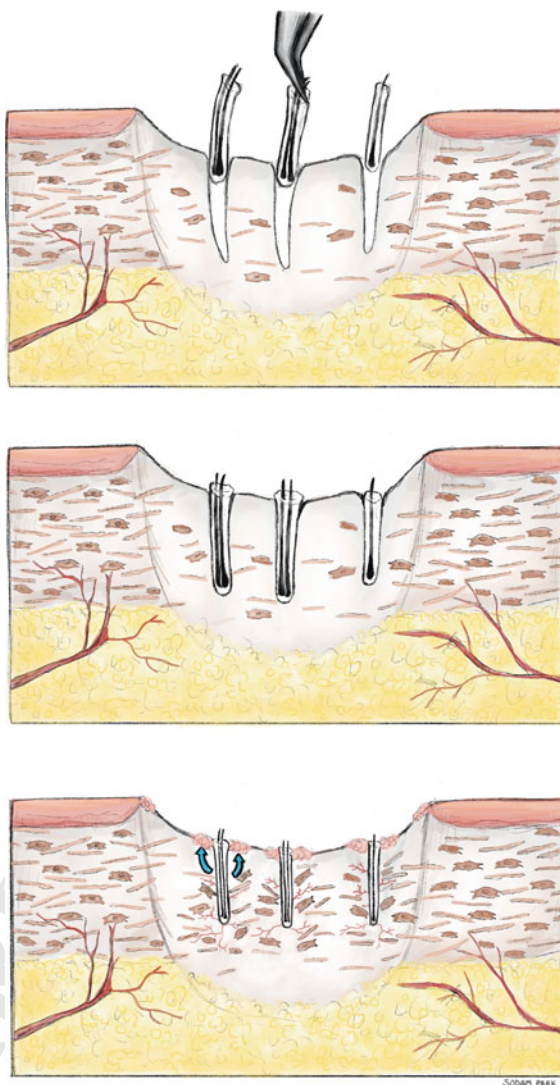
the attribute of "donor dominance", which means that they maintain their original characteristics after transplantation from a donor site to a new region [10]. They regenerate and start cycling, producing hair shafts approximately 2–4 months after their implantation. It is pertinent to say here that, in addition to terminal and vellus hair follicles, the follicular units (FUs) harvested with 1 mm punches may contain other cell types such as perifollicular dermal fibroblasts, dermal adipocytes, and eccrine epithelial cells [11] (Fig. 14.2). Although the contribution of all these extrafollicular cell types in wound healing has been well established [12–16], their relative

Fig. 14.2 Follicular unit harvested from the scalp during a hair transplantation procedure. This FU contain 3 hair follicles (1 terminal and 2 intermediate), perifolicular dermis, sebaceous gland, and adipose tissue. The presence of eccrine coil is not visible unless stained with specific dye such as methelene blue
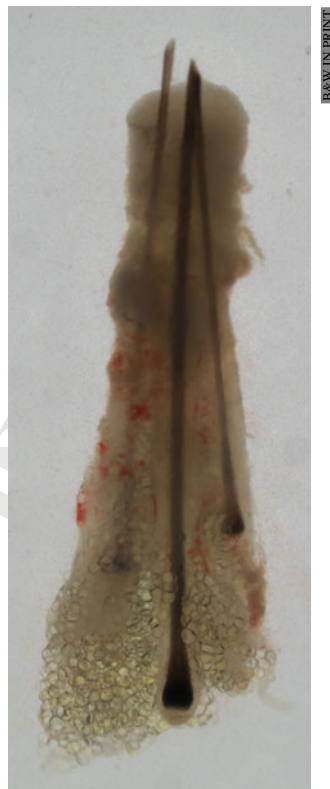
proportion in the skin punches is minor in comparison with the number of follicular cells.

Hair follicle transplantation into wounds is performed under local anesthesia as an outpatient procedure. There are two surgical methods that can be used for hair follicle harvesting: the *follicular unit excision (FUE)* technique, which involves the excision of FUs one at a time using small circular punches, and the strip harvesting method also known as *follicular unit transplantation (FUT)*, which involves excising a strip from the mid-occipital scalp followed by its stereomicroscopic dissection into follicular units. Most published cases of hair transplantation in wounds have used the FUE technique because it is less invasive, and the donor wounds heal by second intention with no need for suturing. However, although in hair restoration surgery the widest punch used in FUE measures 1 mm in diameter, bigger punches of up to 2 mm have been used in transplantation for wound healing because the goal is not to provide a cosmetic natural hair coverage but to provide a source of epithelial and mesenchymal hair follicle cells that migrate into the wound site and stimulate the healing process. The hair follicle grafts are inserted into slits created in the wound bed, the size of which must be sufficient to accommodate the diameter of the hair follicle graft. For example, for the insertion of FU grafts, which normally measure

1 mm in diameter and 4–5 mm in depth, the slits can be made with a 20-gauge needle or a 1 mm surgical blade. The insertion can then be made with fine tip forceps or with hair implanters.

The first pilot study using hair transplant grafts to heal wounds included 10 patients with chronic leg ulcers of 10.5 years average duration and of venous pressure and mixed etiology [17]. Each ulcer had an experimental area that was transplanted with 2 mm punch scalp grafts and a non-transplanted control area. A significant reduction in ulcer size was noted in the experimental area compared with the control, and most patients presented an increase of granulation tissue, decrease of pain, and ulcer border reactivation. After this pilot study in 2012 [17], a further seven papers have been published reporting on the successful use of transplanted hair follicles to stimulate the healing of difficult-to-heal or complex wounds. These papers are summarized in Table 14.1. The following paragraphs describe some of the most important points of interest from these publications.

AQ2

Martinez et al. published a randomized controlled trial of 12 patients with chronic leg ulcers comparing the healing capacity of hair follicle punch scalp grafts versus punch grafts harvested from non-hairy areas [18]. Each ulcer was divided longitudinally into two halves, one half receiving the hair follicle grafts and the other half the same number of grafts with no hair. At the 18-week endpoint a 75% ulcer reduction was observed in the area transplanted with hairy grafts compared with 34% in the area transplanted with non-hairy grafts, demonstrating that grafts containing hair follicles induced a significantly ($P = 0.002$) better healing response (Table 14.2).

AQ3

Another study published by Yang et al. compared the outcomes of 40 chronic wounds, 20 of which were treated with transplanted follicles and 20 with the more conventional therapy of split thickness skin grafts [19]. An interesting observation of this study was that wounds treated with the hair follicles achieved in general a better residual scar quality, which was more elastic and less contracted.

A 54-year-old intermediate recessive dystrophic epidermolysis bullosa patient with chronic ulcers was successfully treated with hair follicle transplantation [20]. This case is particularly interesting from a clinical point of view because the wounds of this congenital disease due to mutations in the COL7A1 gene are very recalcitrant and have a high risk of developing squamous cell carcinomas as result of poor wound healing. These patients suffer from skin fragility, blistering, and chronic non-healing ulcers from infancy and current treatments are mostly supportive. In this particular patient, a total of 360 follicular units were transplanted in nine sessions over 5 years, resulting in rapid healing of most of the treated ulcers. This novel indication of using hair follicles as a treatment of epidermolysis bullosa and other blistering diseases seems to be promising, especially since a recent publication has also demonstrated the key role of hair follicles stem cells in the healing of subepidermal blisters produced in mice [21].

It is also interesting to note that in several of the publications the authors described that the hairs transplanted in the wound grew in far less quantity than would be expected in a normal hair transplant procedure performed in androgenetic alopecia [19, 22], sometimes growing in different patterns in the central and peripheral zones

Table 14.1 Publications showing hair transplantation as a therapy for wound healing

Patients/type of wound treated	Procedure	Outcome	Reference
1 patient with full thickness burn on the scalp	Artificial skin (Integra) followed by autologous scalp hair follicle transplantation 12 days later	Complete re-epithelialization	Navsaria et al. [8]
2 patients with scalp defects	Artificial dermis in the first phase until granulation; then hair graft transplantation	Complete healing	Narushima et al. [9]
15 patients with third-degree burns on limbs and hands	Hair follicle containing dermal grafts from scalp	Complete re-epithelialization	Zakine et al. [7]
10 patients with chronic venous leg ulcers	Hair transplantation (2 mm punch)	At 18 weeks, 27% reduction in transplanted area compared with 6% reduction in the non-transplanted control area Transplanted area increased in granulation tissue	Jimenez et al. [17]
14 patients with chronic wounds	Hair transplantation. No control group	Complete healing in all patients after 2 months	Liu et al. [22]
40 patients with traumatic or surgical wounds	20 patients treated with hair grafts and 20 treated with split thickness skin grafts	Better skin/scar quality and clinical outcome was found in the ulcers treated with hair follicle grafts	Yang et al. [19]
12 patients with chronic venous leg ulcers	2 mm punch hair transplant. Half of the ulcer transplanted with punch scalp hair grafts and the other half with punch skin grafts from non-hairy abdominal skin	At 18 week end point of the study, 75% ulcer area reduction in the side of transplanted hair versus 34% reduction in the side of non-hairy grafts	Martínez et al. [18]
1 patient with chronic leg ulcer	One third of the ulcer was transplanted with scalp hair grafts, one third with skin grafts from the back, and one third served as control	The area transplanted with scalp graft healed significantly better	Fox et al. (2016)

(continued)

Table 14.1 (continued)

Patients/type of wound treated	Procedure	Outcome	Reference
15 patients with chronic leg ulcers	Hair follicular unit transplant	At 18 week end-point of the study, average ulcer area improved by 49% and volume by 72%. Two patients did not respond	Budamakuntla et al. (2017)
2 patients with non-healing traumatic and iatrogenic ulcers	Hair follicular unit transplant	Ulcers completely healed	Alam et al. [23]
1 patient with dystrophic epidermolysis bullosa and non-healing ulcers	Hair follicular unit transplant	Most treated ulcers healed completely. 360 follicular units transplanted in 9 sessions over 5 years	Wong et al. [20]

Table 14.2 Clinical response after hair follicle transplantation in wounds

1	Overall faster and greater healing response (significant wound reduction)
2	Increased re-epithelialization from the borders (wound border reactivation) and from the transplanted follicles
3	Decrease in pain
4	Greater development of granulation tissue
5	Better skin/scar quality (more elastic and less contracted scar)

of the wounds [23]. This would seem to support the idea that the wound microenvironment dictates the fate of the transplanted hair follicles in the direction of wound healing and not in the direction of hair shaft production, a hypothesis suggested by Jahoda in 2001 [24, 25].

Hair Follicles and Wound Healing: Experimental Studies

Years after the publication of Bishop's study, there exists an increasing body of evidence describing the role of hair follicles in wound healing. As mentioned above, experimental studies using transgenic mouse models demonstrated that bulge stem cells migrate out of the follicle in response to an injury to the skin, differentiate into epidermal progenitor cells, and contribute to the restoration of the epidermis [5, 26, 27]. Lineage tracing in mouse skin confirmed that hair follicle stem cells contribute to the healing of wounds at the expense of hair development, causing a delay in hair follicle growth [21]. Hair follicles, rather than the interfollicular epidermis, were also shown to be the primary source of keratinocytes for the repair of blister

wounds, which caused reduction in the hair follicle size. Accordingly, in the absence of hair follicles, there is a significant delay in re-epithelialization during the healing of murine wounds [28].

Besides the epidermal compartment of the hair follicle, the hair follicle mesenchyme also appears to participate in the wound healing response [25, 29, 30]. Lineage studies in mice demonstrated that alongside the skin-derived precursors (SKPs), hair follicle dermal stem cells, as well as dermal papilla and dermal sheath cells from follicles surrounding the site of injury are mobilised to migrate into the wound bed and support skin repair [31]. When injected into the site of skin injury, dermal stem cells repopulate full-thickness wounds, simultaneously rejuvenating hair follicle growth [31]. Similarly, dermal sheath cells were shown to have an ability to both reconstitute the hair follicle mesenchyme and generate interfollicular dermal fibroblasts after transplantation [29]. Importantly, the clinical potential of dermal cell populations lies in their ability to be expanded in vitro, whilst maintaining the capacity to give rise to various mesenchymal cell types [31]. Although there is strong evidence that follicular cells can migrate to support wound healing, lineage tracing and single-cell studies examining the long-term fate and progeny of these cells will be essential to understand the full potential of their contribution to the repair of wounds.

Importantly, it is not only the presence of hair follicles, but also the stage of the cycle that impact on the wound healing capacity of the skin. Mouse wounding studies demonstrated that skin containing hair follicles in an active anagen stage heal faster than skin with hair follicles in a resting telogen stage [32]. Alongside accelerated healing, the presence of anagen hair follicles was linked with faster re-epithelialization, increased angiogenesis, and deposition of extracellular matrix in the dermis [32].

A phenomenon of wound-induced hair neogenesis (WIHN) provides further evidence for the link between hair follicle growth and wound healing. In the mouse model of WIHN, large-size excisional skin wounds can heal by activating spontaneous regeneration of new hair follicles in the wound centre [33]. In the process, myofibroblasts transdifferentiate into adipocytes, reducing the formation of fibrotic tissue, with the conversion triggered by hair follicle-derived BMP (bone morphogenic protein) signals [13]. Similarly, in a coculture system, human scalp follicles induced BMP4-dependent trans differentiation of human keloid fibroblasts into adipocytes, suggesting a potential of hair follicles to benefit the wound healing response, as well as reducing the formation of scars [13].

Hair Follicles and Skin Remodelling: Future Benefits

During the hair follicle cycle, the healthy interfollicular skin undergoes constant physiological remodelling, which can be clearly observed in mouse skin where follicles grow synchronously with one another [34, 35]. When murine hair follicles are in anagen, the epidermis, dermis, and hypodermis (adipose tissue) are respectively

229 2.0-, 1.6-, and 1.7-fold thicker compared to when all follicles are in telogen [36].
230 Despite fluctuations in dermal thickness, the number of cells in the dermis remains
231 constant during the cycle [37, 38]. This raises the interesting possibility that changes
232 to dermal thickness can be linked to a redistribution of the extracellular matrix to
233 accommodate the growth of follicles during anagen [39]. Skin vasculature also varies
234 with the stage of the hair follicle cycle, with angiogenesis occurring around growing
235 hair follicles (anagen) followed by degeneration of capillaries when hair follicles
236 regress (catagen) [40–42].

237   While hair follicle cycling and remodelling of interfollicular skin occur at the
238 same time, it is not clear whether the skin changes drive the hair follicle cycle or if
239 the transition through hair follicle stages induces changes to the skin. In support of
240 the former hypothesis, a functional analysis of mouse skin revealed that intradermal
241 adipocytes are necessary and sufficient to drive follicular stem cell activation and
242 induction of anagen, while adipocyte defects result in reduced hair growth [43].
243 Similarly, neurons surrounding the hair follicle were found to interact with bulge cells
244 via release of paracrine factors, changing the lineage of bulge cells into epidermal
245 stem cells [44]. These two studies raised the possibility that other cell types residing in
246 the interfollicular skin may provide molecular input that could direct the hair follicle
247 cycle. On the other hand, there is substantial evidence that cycling hair follicles
248 induce the growth of vascularization and innervation in the interfollicular zone [40–
249 42]. Among others, several in vitro and in vivo studies described the pro-angiogenic
250 properties of the hair follicle, including the expression of VEGF (vascular endothelial
251 growth factor) in various follicular compartments [45–48]. A possible explanation
252 for the observed effect could be a bi-directional independence whereby cycling hair
253 follicles influence remodelling of the interfollicular skin, while the interfollicular
254 skin has the capacity to induce transition of the follicle through the cycle, depending
255 on the strength of the induced effect and timing of the cycle stage.

256   Besides inducing changes to healthy skin during a natural hair cycle and
257 contributing to the wound healing response, it remains to be investigated whether
258 hair follicles could also remodel the fibrotic tissue formed after skin injuries. In
259 fact, anecdotal unpublished observations by hair surgeons have noted the clinical
260 aesthetic improvement of scalp scars (mainly burn scars and scars from split thick-
261 ness skin grafts) as a result of hair transplantation (scientific poster presented by Dr.
262 Richard Keller at ISHRS meeting in Montreal, 2008). Thus, it could be possible that
263 anagen hair follicles transplanted into scars could remodel mature scars, similar to
264 how they remodel healthy tissue, with an increase in the thickness of skin layers,
265 vascularization, adipogenesis, and innervation of the fibrotic tissue. This effect could
266 be facilitated by either migration of epidermal and dermal stem cells out of hair folli-
267 cles to support skin remodelling, or the release of remodelling factors directly from
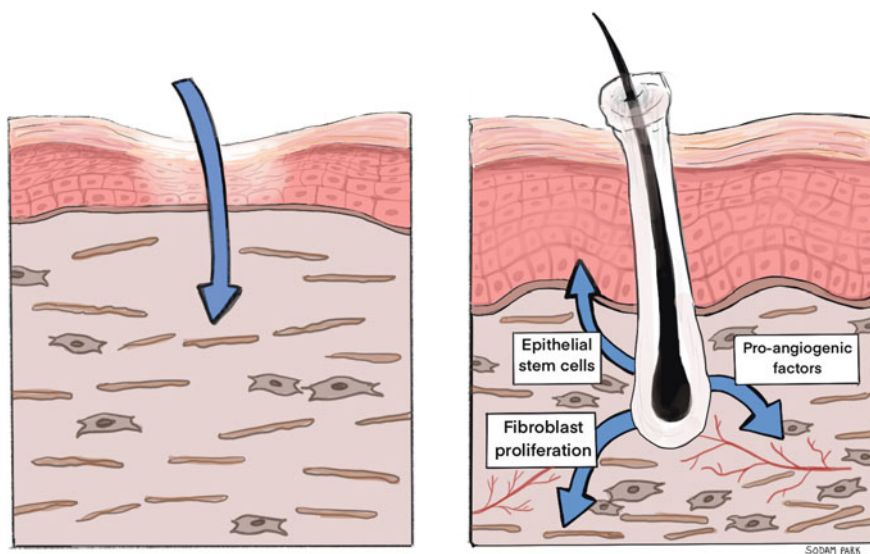268 the follicle (Fig. 14.3).

Fig. 14.3 Hair follicle transplantation into scars. We hypothesize that anagen hair follicles transplanted into scars could remodel mature scars, similar to how they remodel healthy interfollicular tissue

Concluding Remarks

Hair follicle transplantation for wound healing applications is a relatively recent and still underutilized minimally invasive surgical technique. It is a safe and relatively inexpensive procedure that does not require cell manipulation in the laboratory. The clinical indications, which currently have been limited to stimulate the healing of difficult-to-heal wounds or chronic ulcers, will become better defined as further clinical experience is gained with this form of therapy. However, there remain important questions to be answered, including the minimum number of hair follicles to be transplanted in the wound bed per cm^2 in order to reach an optimal healing response.

Once we understand the exact mechanism behind the role of hair follicles in wound healing and scar remodelling, we can try to mimic the effect of hair follicles on skin repair and regeneration with therapeutic solution. A potential approach involves deciphering the populations of hair follicle cells that contribute to the observed effect and injecting them directly into wounds or scar tissue in order to improve the clinical outcomes. Alternatively, elucidating the paracrine effect of transplanted follicles would open up new avenues for therapeutic discovery, to replicate the combination of required factors that facilitate healing or scar remodelling.

References

1. Brown J, McDowell F (1942) Epithelial healing and the transplantation of skin. Ann Surg 115(6):1166–1181
2. Bishop GH (1945) Regeneration after experimental removal of skin in man. Am J Anat (2):153–181
3. Mimoun M, Chaouat M, Picovski D, Serroussi D, Smarrito S (2006) The scalp is an advantageous donor site for thin-skin grafts: a report on 945 harvested samples. Plast Reconstr Surg 118(2):369–373
4. Weyandt G, Bauer B, Berens N, Hamm H, Broecker E (2009) Split-skin grafting from the scalp: the hidden advantage. Dermatol Surg 35(12):1873–1879
5. Ito M, Liu Y, Yang Z, Nguyen J, Liang F, Morris RJ et al (2005) Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis. Nat Med 11(12):1351–1354
6. Nuutila K (2019) Hair follicle transplantation for wound repair. Adv Wound Care 10(3):153–163
7. Zakine G, Mimoun M, Pham J, Chaouat M (2012) Reepithelialization from stem cells of hair follicles of dermal graft of the scalp in acute treatment of third-degree burns: first clinical and histologic study. Plast Reconstr Surg 130(1)
8. Navsaria H, Ojeh N, Moiemen N, Griffiths M, Frame J (2004) Reepithelialization of a full-thickness burn from stem cells of hair follicles micrografted into a tissue-engineered dermal template (Integra). Plast Reconstr Surg 113(3):978–981
9. Narushima M, Mihara M, Yamamoto Y, Iida T, Koshima I, Matsumoto D (2011) Hair transplantation for reconstruction of scalp defects using artificial dermis. Dermatol Surg 37(9):1348–1350
10. Orentreich N (1959) Autografts in alopecias and other selected dermatological conditions. Ann N Y Acad Sci 83(3):463–479
11. Poblet E, Jimenez F, Escario-Travesedo E, Hardman JA, Hernández-Hernández I, Agudo-Mena JL et al (2018) Eccrine sweat glands associate with the human hair follicle within a defined compartment of dermal white adipose tissue. Br J Dermatol 178(5):1163–1172
12. Shook BA, Wasko RR, Mano O, Rutenberg-Schoenberg M, Rudolph MC, Zirak B et al (2020) Dermal adipocyte lipolysis and myofibroblast conversion are required for efficient skin repair. Cell Stem Cell 26(6):880–895
13. Plikus MV, Guerrero-Juarez CF, Ito M, Li YR, Dedhia PH, Zheng Y et al (2017) Regeneration of fat cells from myofibroblasts during wound healing. Science (80)8792:1–12
14. Schmidt BA, Horsley V (2013) Intradermal adipocytes mediate fibroblast recruitment during skin wound healing. Development 140(7):1517–1527
15. Chan CKF, Longaker MT (2017) Fibroblasts become fat to reduce scarring: pathologic scarring could be avoided by manipulating fibroblast plasticity. Science 355(6326):693
16. Rittié L, Sachs D, Orringer J, Voorhees J, Fisher G (2013) Eccrine sweat glands are major contributors to reepithelialization of human wounds. Am J Pathol 182(1):163–171
17. Jimenez F, Garde C, Poblet E, Jimeno B, Ortiz J, Martínez ML et al (2012) A pilot clinical study of hair grafting in chronic leg ulcers. Wound Repair Regen 20(6):806–814
18. Martínez M-L, Escario E, Poblet E, Sanchez D, Buchon F-F, Izeta A et al (2016) Hair follicle-containing punch grafts accelerate chronic ulcer healing: a randomized controlled trial. J Am Acad Dermatol 75(5):1007–1014
19. Yang Z, Liu J, Zhu N, Qi F (2015) Comparison between hair follicles and split-thickness skin grafts in cutaneous wound repair. Int J Clin Exp Med 8(9):15822–15827
20. Wong TW, Yang CC, Hsu CK, Liu CH, Yu-Yun Lee J (2020) Transplantation of autologous single hair units heals chronic wounds in autosomal recessive dystrophic epidermolysis bullosa: a proof-of-concept study. J Tissue Viability 30(1):36–41
21. Fujimura Y, Watanabe M, Ohno K, Kobayashi Y, Takashima S, Nakamura H et al (2021) Hair follicle stem cell progeny heal blisters while pausing skin development. EMBO Rep 22(7):e50882

22. Liu J-Q, Zhao K-B, Feng Z-H, Qi F-Z (2015) Hair follicle units promote re-epithelialization in chronic cutaneous wounds: a clinical case series study. Exp Ther Med 10(1):25

23. Alam M, Cooley J, Plotczyk M, Martínez-Martín MS, Izeta A, Paus R et al (2019) Distinct patterns of hair graft survival after transplantation in 2 nonhealing ulcers. Dermatol Surg 45(4):557–565

24. Aamar E, Avigad Laron E, Asaad W, Harshuk-Shabso S, Enshell-Seijffers D (2021) Hair-follicle mesenchymal stem cell activity during homeostasis and wound healing. J Invest Dermatol

25. Jahoda CAB, Reynolds AJ (2001) Hair follicle dermal sheath cells: unsung participants in wound healing. Lancet 358:1445–1448

26. Levy V, Lindon C, Zheng Y, Harfe B, Morgan B (2007) Epidermal stem cells arise from the hair follicle after wounding. FASEB J 21(7):1358–1366

27. Heidari F, Yari A, Rasoolijazi H, Soleimani M, Dehpoor A, Sajedi N et al (2016) Bulge hair follicle stem cells accelerate cutaneous wound healing in rats. Wounds 28(4):132–141

28. Langton AK, Herrick SE, Headon DJ (2008) An extended epidermal response heals cutaneous wounds in the absence of a hair follicle stem cell contribution. J Invest Dermatol 128(5):1311–1318

29. Biernaskie J, Paris M, Morozova O, Fagan BM, Marra M, Pevny L et al (2009) SKPs derive from hair follicle precursors and exhibit properties of adult dermal stem cells. Cell Stem Cell 5(6):610–623

30. Gharzi A, Reynolds A, Jahoda C (2003) Plasticity of hair follicle dermal cells in wound healing and induction. Exp Dermatol 12(9):126–136

31. Agabalyan NA, Rosin NL, Rahmani W, Biernaskie J (2017) Hair follicle dermal stem cells and skin-derived precursor cells: exciting tools for endogenous and exogenous therapies. Exp Dermatol 26(6):505–509

32. Ansell DM, Kloepper JE, Thomason HA, Paus R, Hardman MJ (2011) Exploring the "hair growth-wound healing connection": anagen phase promotes wound re-epithelialization. J Invest Dermatol 131(2):518–528

33. Ito M, Yang Z, Andl T, Cui C, Kim N, Millar SE et al (2007) WNT-dependent de novo hair follicle regeneration in adult mouse skin after wounding. Nature 447(7142):316–320

34. Jahoda CAB, Christiano AM (2011) Niche crosstalk: intercellular signals at the hair follicle. Cell 146(5):678–681

35. Plikus MV, Chuong CM (2008) Complex hair cycle domain patterns and regenerative hair waves in living rodents. J Invest Dermatol 128(5):1071–1080

36. Hansen LS, Coggle JE, Wells J, Charles MW (1984) The influence of the hair cycle on the thickness of mouse skin. Anat Rec 210(4):569–573

37. Joost S, Annusver K, Jacob T, Sun X, Dalessandri T, Sivan U et al (2020) The molecular anatomy of mouse skin during hair growth and rest. Cell Stem Cell 26(3):441–457

38. Chase HB, Montagna W, Malone JD (1953) Changes in the skin in relation to the hair growth cycle. Anat Rec 116(1):75–81

39. Moffat GH (1968) The growth of hair follicles and its relation to the adjacent dermal structures. J Anat 102:527–540

40. Durward A, Rudall KM (1958) The vascularity and patterns of growth of hair follicles. Biol Hair Growth 189–218

41. Mecklenburg L, Tobin DJ, Müller-Röver S, Handjiski B, Wendt G, Peters EMJ et al (2000) Active hair growth (anagen) is associated with angiogenesis. J Invest Dermatol 114(5):909–916

42. Ellis RA, Moretti G (1959) Vascular patterns associated with catagen hair follicles in the human scalp. Ann N Y Acad Sci 2125

43. Festa E, Fretz J, Berry R, Schmidt B, Rodeheffer M, Horowitz M et al (2011) Adipocyte lineage cells contribute to the skin stem cell niche to drive hair cycling. Cell 146(5):761–771

44. Brownell I, Guevara E, Bai C, Loomis C, Joyner A (2011) Nerve-derived sonic hedgehog defines a niche for hair follicle stem cells capable of becoming epidermal stem cells. Cell Stem Cell 8(5):552–565

45. Yano K, Brown LF, Detmar M (2001) Control of hair growth and follicle size by VEGF-mediated angiogenesis. J Clin Invest 107(4):409–417
46. Kozlowska U, Blume-Peytavi U, Kodelja V, Sommer C, Goerdt S, Majewski S et al (1988) Expression of vascular endothelial growth factor (VEGF) in various compartments of the human hair follicle. Arch Dermatol Res 290(12):661–668
47. Lachgar S, Moukadiri H, Jonca F, Charveron M, Bouhaddioui N, Gall Y et al (1996) Vascular endothelial growth factor is an autocrine growth factor for hair dermal papilla cells. J Invest Dermatol 106(1):17–23
48. Bassino E, Gasparri F, Giannini V, Munaron L (2015) Paracrine crosstalk between human hair follicle dermal papilla cells and microvascular endothelial cells. Exp Dermatol 24(5):388–390

Author Queries

Query Refs.	Details Required	Author's response
AQ1	Kindly note that a structured abstract is not allowed, so we have processed the single paragraph. Please check and confirm.	
AQ2	References 'Budamakuntla et al. (2017), Fox et al. (2016)' are cited in the text but not provided in the reference list. Please provide the respective references in the list or delete these citations.	
AQ3	Please check and confirm if the inserted citation of Table 14.2 is correct. If not, please suggest an alternate citation. Please note that tables should be cited sequentially in the text.	

MARKED PROOF

Please correct and return this set

Please use the proof correction marks shown below for all alterations and corrections. If you wish to return your proof by fax you should ensure that all amendments are written clearly in dark ink and are made well within the page margins.

Instruction to printer	Textual mark	Marginal mark
Leave unchanged	··· under matter to remain	Ⓙ
Insert in text the matter indicated in the margin	⋏	New matter followed by ⋏ or ⋏②
Delete	/ through single character, rule or underline or ⊢——⊣ through all characters to be deleted	⌀ or ⌀②
Substitute character or substitute part of one or more word(s)	/ through letter or ⊢——⊣ through characters	new character / or new characters /
Change to italics	— under matter to be changed	⌣
Change to capitals	≡ under matter to be changed	≡
Change to small capitals	= under matter to be changed	=
Change to bold type	∼ under matter to be changed	∼
Change to bold italic	≈ under matter to be changed	≋
Change to lower case	Encircle matter to be changed	≢
Change italic to upright type	(As above)	⊥
Change bold to non-bold type	(As above)	⊥
Insert 'superior' character	/ through character or ⋏ where required	Y or ⋏ under character e.g. Y² or ⋏²
Insert 'inferior' character	(As above)	⋏ over character e.g. ⋏₂
Insert full stop	(As above)	⊙
Insert comma	(As above)	,
Insert single quotation marks	(As above)	Y or ⋏ and/or Y or ⋏
Insert double quotation marks	(As above)	Y or ⋏ and/or Y or ⋏
Insert hyphen	(As above)	⊢⊣
Start new paragraph	⌐	⌐
No new paragraph	⌒	⌒
Transpose	⊔⊓	⊔⊓
Close up	linking ⌣ characters	⌒
Insert or substitute space between characters or words	/ through character or ⋏ where required	Y
Reduce space between characters or words	| between characters or words affected	↑