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Review

Epithelial stem cells and implications for wound repair

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ABSTRACT

Activation of epithelial stem cells and efficient recruitment of their proliferating progeny plays a critical role in cutaneous wound healing. The reepithelialized wound epidermis has a mosaic composition consisting of progeny that can be traced back both to epidermal and several types of hair follicle stem cells. The contribution of hair follicle stem cells to wound epidermis is particularly intriguing as it involves lineage identity change from follicular to epidermal. Studies from our laboratory show that hair follicle-fated bulge stem cells commit only transient amplifying epidermal progeny that participate in the initial wound re-epithelialization, but eventually are outcompeted by other epidermal clones and largely disappear after a few months. Conversely, recently described stem cell populations residing in the isthmus portion of hair follicle contribute long-lasting progeny toward wound epidermis and, arguably, give rise to new interfollicular epidermal stem cells. The role of epithelial stem cells during wound healing is not limited to regenerating stratified epidermis. By studying regenerative response in large cutaneous wounds, our laboratory uncovered that epithelial cells in the center of the wound can acquire greater morphogenetic plasticity and, together with the underlying wound dermis, can engage in an embryonic-like process of hair follicle neogenesis. Future studies should uncover the cellular and signaling basis of this remarkable adult wound regeneration phenomenon.

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Contents

1. Introduction

Skin epithelium is comprised of epidermis and appendages such as the hair follicle. Both epidermis and hair follicles show significant

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regenerative potential during their physiological renewal. Epidermis regenerates in a steady state *via* balanced proliferation of basal cells and shedding of cornified squamous cells at its surface. Hair follicles regenerate *via* a complex cyclical process. This cycle starts with the activation of stem cells, followed by proliferation and differentiation of their progeny. It terminates with apoptotic involution, during which most of the epithelial lineages expanded from hair follicle stem cells at the beginning of the cycle are eliminated. Stem cells themselves survive this apoptotic involution, and regenerate the lost portion of the hair follicle in the next new growth cycle.

Unlike physiological renewal, regeneration of the skin after wounding was historically thought to be only partial, limited to the formation of stratified epidermis over the dermal scar. However, recent findings from our laboratory show that more complete skin regeneration during wound healing is possible. New hair follicles regenerate in the center of large cutaneous wounds *via* a process that resembles their normal embryonic development [1]. These findings warrant new inquiries into the true morphogenetic potential of adult epithelial stem cells during wound repair. Therefore, this review will focus on what is currently known about the contribution of various epithelial stem cells to wound healing. It will also introduce the emerging field of embryonic-like wound regeneration.

2. Diversity of epithelial stem cells in the skin

Restoration of skin barrier function is the key priority during wound repair. This is accomplished *via* rapid re-epithelialization, when the wound becomes covered with the new stratified epidermis. Interestingly, numerous distinct stem cell populations become activated during the healing process and are recruited into the wound. To understand the significance of contribution from these various epithelial stem cells, first we will briefly discuss their physiological heterogeneity and anatomical distribution in the skin.

Epithelial stem cells, in general, fit a broader definition of adult somatic stem cells, as they are quiescent but self-renew and differentiate into at least one type of progeny. Historically, scores of epithelial stem cell populations were identified based on various *in vitro* and *in vivo* methods. However, recently, it has become apparent that many of these likely represent only a few distinct stem cell types.

2.1. Interfollicular epidermal stem cells

Physiological renewal of the epidermis is supported by proliferation of cells in its basal layer, and normally does not require additional support from epithelial appendages, such as hair follicles [20,2,3]. Since epidermal renewal continues throughout one's lifetime, it has been postulated that at least a portion of epidermal basal cells behave like stem cells. Historically, the favored model has been that basal layer stem cells give rise to transiently amplifying progeny that, in turn, undergo a limited number of divisions to generate the upper strata of the epidermis [4,5]. According to this model, each stem cell generates an epidermal clone, termed the Epidermal Proliferative Unit (EPU) [6–8]. The size of each EPU is thought to be constrained to a limited number of cell divisions prior to terminal differentiation. The entire epidermal sheet is thus maintained by a collection of co-existing steady state EPUs with one stem cell at the center of each of them. Experimental support for the EPU model of epidermal organization came from mouse studies where a replication-deficient retroviral vector was used to genetically mark epidermal cells at low frequency. In these experiments, discreet vertical columns of labeled keratinocytes reminiscent of hypothetical EPUs could be seen to arise from the basal layer [8]. Further support for the EPU-based epidermal organization came from the pulse-chase labeling studies that revealed the presence of a small number of quiescent, label-retaining cells scattered throughout the basal layer [9–11].

In recent years, the EPU model has been challenged. Using a low frequency inducible *Cre* genetic model, Clayton et al. [12] and Doupe et al. [13] were able to mark and analyze the fate of individual proliferating basal cells after a period of over one year. In contradiction to the canonical EPU model, which predicts the size of each EPU to be finite, it was shown that some epidermal clones continuously expand in size, while others shrink and disappear, and yet others behave like typical EPUs (reviewed in [14]). Mathematical modeling of these variable clone patterns suggested a stochastic model for epidermal renewal, in which each proliferating basal cell can give rise to two new proliferating basal cells, two differentiated progeny or both [12]. According to this Committed Progenitor (CP) model, epidermis is maintained by a uniform population of basal progenitors that undergo stochastically distributed symmetric divisions to maintain the basal layer and asymmetric divisions to generate more differentiated progeny [15]. In support of this model, recent data shows that a single basal epidermal cell can indeed divide both symmetrically to produce two new basal cells and asymmetrically to generate more differentiated progeny [16].

Whether epidermal renewal strictly follows either EPU or CP model still remains a subject of debate [10,11,17]. In an effort to merge these two models, it has been proposed that both committed progenitors and epidermal stem cells co-exist, the first to assure life-long epidermal maintenance and the latter to be marshaled for rapid engagement and proliferation after wounding [17]. Recent study by Mascré et al. [18] has provided experimental evidence that supports this combined model.

2.2. Heterogeneity of hair follicle stem cells

One of the major challenges to the field of cutaneous epithelial stem cell biology derives from the paucity of specific markers for reliable labeling, isolation and fate mapping of distinct stem cell populations. A very different scenario exists for hair follicle stem cells. The discovery of a label-retaining population of cells within the bulge [19] led to the first identification of stem cells within the hair follicle. Lineage tracing studies [20] clearly showed that bulge stem cells regenerate hair follicles during cycling and also contribute to epidermal regeneration in response to wounding. To date, multiple new hair follicle stem cell populations have been described based upon expression of newly defined markers, proliferative potential, skin reconstitution studies and distinct anatomical location along the hair axis (Fig. 1). We will review these populations primarily based upon their location along the hair follicle and lineage potential. Later in this review, we will discuss their contributions to wound repair in more detail.

2.2.1. Bulge

The first group of hair follicle stem cells discovered comprises quiescent cells of the bulge [19]. Since these cells divide infrequently, they retain nucleotide analog labels, such as BrdU, and hence, are known as label-retaining cells. Under physiological conditions, bulge cells mainly contribute to the cycling portion of the anagen hair follicle. Following wounding, they can also contribute, at least transiently, to epidermal repair [20]. In addition to label-retaining methods, bulge stem cells have also been identified on the basis of expression of keratin 15 (Krt15) [21], R-spondin receptor Lgr5 [22], CD34 [23], and transcriptional factors Sox9 [3], Lhx2 [24], Tcf3 [25], Nfatc [26] and Gli1 [27].

Krt15 expression defines a large portion of bulge stem cells [21,28]. Fate-mapping analyses of Krt15+ cells showed their ability to reconstitute all epithelial lineages of the anagen hair follicle

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