

Editorial

Scarless Skin Regeneration- Are we there yet?

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The largest organ in the body, the skin conducts a wide range of functions to support and maintain human health [1,2]. The skin epidermis and its appendages (e.g., hair follicle, sebaceous and sweat glands) provide a protective barrier against physical, chemical and biological pathogens and also prevent dehydration. However, full-thickness skin wounding commonly leads to non-functioning scar formation with substantial loss of skin appendages. Cutaneous scar formation can cause severe cosmetic, functional, and psychological problems. There are more than 87 million patients in the US and Europe that could benefit from scar reduction therapies [3,4]. Despite tremendous efforts to attenuate scarring, the regeneration of perfect skin remains a challenge and highly prized goal [5], and has thus become a major aim in wound healing [5,6].

The complex process of healing adult skin may contribute to current unsatisfactory therapy. Wound healing is one of the most intricate biological processes, which requires the coordinated efforts of various cell lineages, matrix and signaling molecules to work delicately at their hierarchical levels so as to achieve perfect regeneration [6-8]. Normal wound healing encompasses three overlapping but distinct stages, i.e., inflammation, proliferation, and remodeling [9]. Each stage contributes to the overall wound healing effect. However, more and more studies have indicated that the inflammation stage has significant impact on the outcome of wound healing [10].

Although inflammatory responses are indispensable during skin repair, recent studies have shown that they contribute to scar tissue development [10]. Certain mammalian species heal without inflammation or scar formation at early stages of fetal development [11-13]; however, adult skin frequently heals with significant inflammation and non-functional scar formation [14]. This is correlated with the fact that adults have a more mature immune system than a developing fetus. After wound injury, inflammatory cells, including neutrophils, macrophages and mast cells will infiltrate the wound sites gradually. Neutrophils appear shortly after injury and are essential for the clearance of bacteria and both cellular and foreign debris [15], while macrophages produce both inflammatory and angiogenic growth factors [16], such as PDGF BB, TGF- α , TGF- β 1, VEGF, FGF, EGF and IGF-1, which play critical but complex roles for wound healing. Marneros et

al. recently demonstrated that macrophages promote fibroblast scaffold formation in their choroidal neovascularization wound healing model [17]. In the meantime, macrophages also clear excessive neutrophils. Mast cells later will migrate to the wounds and release pro-inflammatory growth factors that also enhance fibrosis synthesis, thus promoting scar formation [14,18]. While these studies clearly illustrate a role for inflammatory infiltrate in wound scar development, reducing inflammation alone will not regenerate a scar-free skin.

Angiogenesis begins at the early stage and is essential for the proliferative stage and the outcome of wound healing [19, 20]. A robust angiogenesis, however, may compromise the cutaneous wound healing and lead to scar formation. Recent study uncovered that scar formation is also regulated by vascular endothelial growth factor (VEGF) levels [21], and the VEGF fluctuation is strongly accompanied with angiogenesis or vascular regression [22]. Wilgus et al. revealed that scarless fetal wounds had lower levels of VEGF and were less vascular than fibrotic fetal wounds, while adding exogenous VEGF could convert the scarless phenotype into a scar-forming phenotype [21]. Such data have led to antiangiogenic therapy to reduce scar formation [22].

Moreover, wound healing outcome is rather tissue-specific [17]. Oral mucosa is generally known to heal without scar formation, and is characterized by faster resolution of inflammation and control of myofibroblast action compared to skin wounds in a pig model [4]. However, the numbers of macrophages, mast cells and other immunopositive cells were significantly lower in the oral mucosal wounds than that in the skin wounds, which is consistent with the aforementioned discussion about the inflammation effect on wound healing. In general, myofibroblasts cause contraction and fibrosis synthesis during skin wound healing. Although the number of myofibroblasts was significantly higher in oral mucosal wounds, the oral mucosal healing showed significantly less contraction as compared with the skin wounds. The synergistic effect of lower inflammatory response and less wound contraction might be the main reason that leads to scarless oral mucosal wound healing. Meanwhile, scar formation likely depends not only on the number of myofibroblasts but also on the extracellular environment

which regulates their function. Horsley et al. recently revealed that the adipose tissue mediates fibroblast migration to promote wound healing [23].

The delicate structure and composition of the extracellular matrix (ECM) are also vital for complete wound healing. African spiny mice are capable of skin autotomy and develop more porous ECM during skin regeneration than non-skin regenerating mice [24]. The slow ECM deposition might allow different molecules to communicate and coordinate to restore the full skin structure. Additionally, the skin regenerating ECM was dominated by collagen type III, while the scar formation ECM was rich in collagen type I, which antagonizes skin appendage regeneration [25].

Although research has elucidated many details of the basic wound healing process, the various factors and differences in wound healing mechanisms make the treatment rather challenging. It is impossible to counteract all scar-forming factors during the treatment. From the treatment point of view, however, an ideal wound scaffold should protect the wound from bacterial infection, control evaporative water loss and prevent dehydration, allow diffusion of oxygen and carbon dioxide, absorb wound exudate, and provide cells an environment similar to native niche to maintain cell phenotype to promote complete skin repair [26].

Our recent study has demonstrated that a dextran-based hydrogel devoid of growth factors and stem cells promoted dermal regeneration with complete skin appendages on a third degree burn injury [27]. The dextran hydrogel might have induced signaling molecules and activated stem cells that helped reconstruct the embryonic skin niche for intact skin regeneration. Although much is still unknown about how dextran scaffold coordinates cell lineages to regenerate complete skin structures, it provides us a rare opportunity to understand how to improve our design of hydrogel scaffolds for deep dermal wound healing. On the basis of our findings, more efficient and personalized hydrogel scaffolds may be developed to further translational medicine.

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