Editorial

Epigenetic regulations on skin wound healing: implications from current researches

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Skin wound healing is a complex biological process including three stages: inflammation, new tissue formation, and remodeling (1). During this process, keratinocytes and dermal cells proliferate and migrate to the wound to participate in the repair, followed in larger wound healing by trichogenesis.

Epigenetics is defined as the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence (2). Epigenetic regulation is very important for embryonic stem cell pluripotency and differentiation, but its roles in adult stem cells, especially skin stem cells participating in wound repair, are largely unclear. To answer this question, a recent paper by Plikus *et al*. reviewed epigenetic control of skin and hair regeneration after wounding (3).

The authors reviewed the epigenetic changes at the wound edge after full thickness punch published in an article by Shaw and Martin [2009]. After the injury, PRC2 components *Ezh2* and *Eed* were rapidly and stably downregulated even after complete reepithelialization and, concomitantly, histone demethylases *Utx* and *Jmjd3* were transiently upregulated in early wounding, so that the chromatin can be transformed into an "open" state. Nevertheless, Lewis *et al*. find that histone deacetylases HDAC1 and HDAC2 are expressed in human migrating wound epithelial tongue during skin regeneration (4), indicating, combined with the reviewed data that HDAC1/2$^{-/-}$ mouse showed complete disruption of epidermal and hair follicle development, the tight epigenetic control of the chromatin structure during this process. Ezhkova *et al*. found that the deletion of H3K27 methyltransferases *Ezh1* and *Ezh2* arrested hair follicle morphogenesis, and hair follicles degenerated due to defective proliferation and increased apoptosis; *Ezh1/2*-null skin also showed slow wound closure during the repair (5). Compared with controls, mice treated with DNA methyltransferase (DNMT) inhibitor 5-aza-2'-deoxycytidine and HDAC inhibitor trichostatin A showed enhanced digital regeneration after digital amputation because of stimulated cell proliferation at the amputation site (6), implicating the effect of epigenetic regulation on cell proliferation during wound healing.

As the authors point out, there are many works focusing on the epigenetic mapping and functional studies of homeostatic skin stem cells (7), but less on that of stem cells in wound healing. Ito *et al*. [2005] find that after epidermal injury, hair follicle bulge stem cells are recruited, migrate in a linear manner toward the center of the wound and acquire an epidermal phenotype but are finally eliminated from the epidermis over several weeks, indicating that bulge stem cells respond rapidly to epidermal wounding by generating short-lived "transient amplifying" cells responsible for acute wound repair (8). The epigenetic changes from "stemness" to "transient amplifying" status are not yet unveiled. Their following work finds that after full-thickness back skin excision, hair follicles regenerated at the healed wound in genetically normal adult mice. However, evidence reveals that the regenerated hair follicles are derived from the non-bulge stem cells but possess a functional stem cell population (9). Further investigation is also needed to elucidate the reason why these epidermal cells in the wound assume a hair follicle stem cell phenotype. In another hand, our and others

works found that using silicon chamber, hair follicle stem cells mixed with dermal fibroblasts reconstituted haired skin (10,11), demonstrating that besides hair follicle regeneration, hair follicle stem cells possess the capacity to differentiate into epidermal cells. Taken these works together, from the standpoint of epigenetics, it could be assumed that between hair follicle stem cells and epidermal cells, there may be a balance of epigenetic modification, according to the extent of which, specific gene loci are in "open" or "compact" pattern under different physiological and pathological conditions, therefore expression of genes are regulated and then cells are categorized into different types, exhibiting different functional phenotype.

Because of the paucity of researches on this area, the authors discussed the myofibroblast induction, which is helpful for understanding dermal remodelling. Fibrogenesis is a critical step during which the scar tissue is formed to prevent further damage and microorganism infection. Myofibroblasts play a central role in wound contraction and fibrosis. They are rare in uninjured tissues but are generated in response to trauma, inflammation or infection (12). Glenisson *et al.* found that HDAC4 is required for transforming growth factor beta-1 (TGFβ-1)-mediated transdifferentiation from fibroblasts to myofibroblasts (13). In addition to pericytes and dermal fibroblasts discussed, evidences demonstrate that fibrocytes are likely an origin of myofibroblasts (14,15).

It is also worth noting that angiogenesis is one of the key processes of skin wound repair. Vascular endothelial growth factor (VEGF) signaling, which is critical for vascular morphogenesis, is under epigenetic regulation. HDAC inhibitors trichostatin A and suberoylanilide hydroxamic acid showed anti-angiogenic effect through altering VEGF signaling (16); and VEGF-mediated down-regulation of miR-101 causes angiogenic effects through reduced repression of *Ezh2* (17).

Epigenetic control in cancer initiation is also reviewed because physiological process of wound healing shares some similarities with cancer metastasis. In fact, evidences have proved that wounding stimulates hair follicle stem cells to participate and promote the growth of basal cell carcinoma (BCC) (18,19). BCCs are associated with misactivation of Hedgehog (Hh) signaling. Wong and Reiter find that expression of an activated form of Smo by stem cells of the hair-follicle bulge and secondary hair germ does not induce robust Hh signaling or produce BCCs, however, wounding recruits hair follicle stem cells from the follicle to the wound site, where downstream Hh signal transduction is derepressed, giving rise to BCC-like tumors (19). Given that hair follicle stem cells participate in wound repair, there is a considerable possibility that their behaviors are tightly controlled by epigenetic regulation, and those stem cells out of control may lead to carcinomas.

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Footnote

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