CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Cellular Memories — More Than Skin Deep

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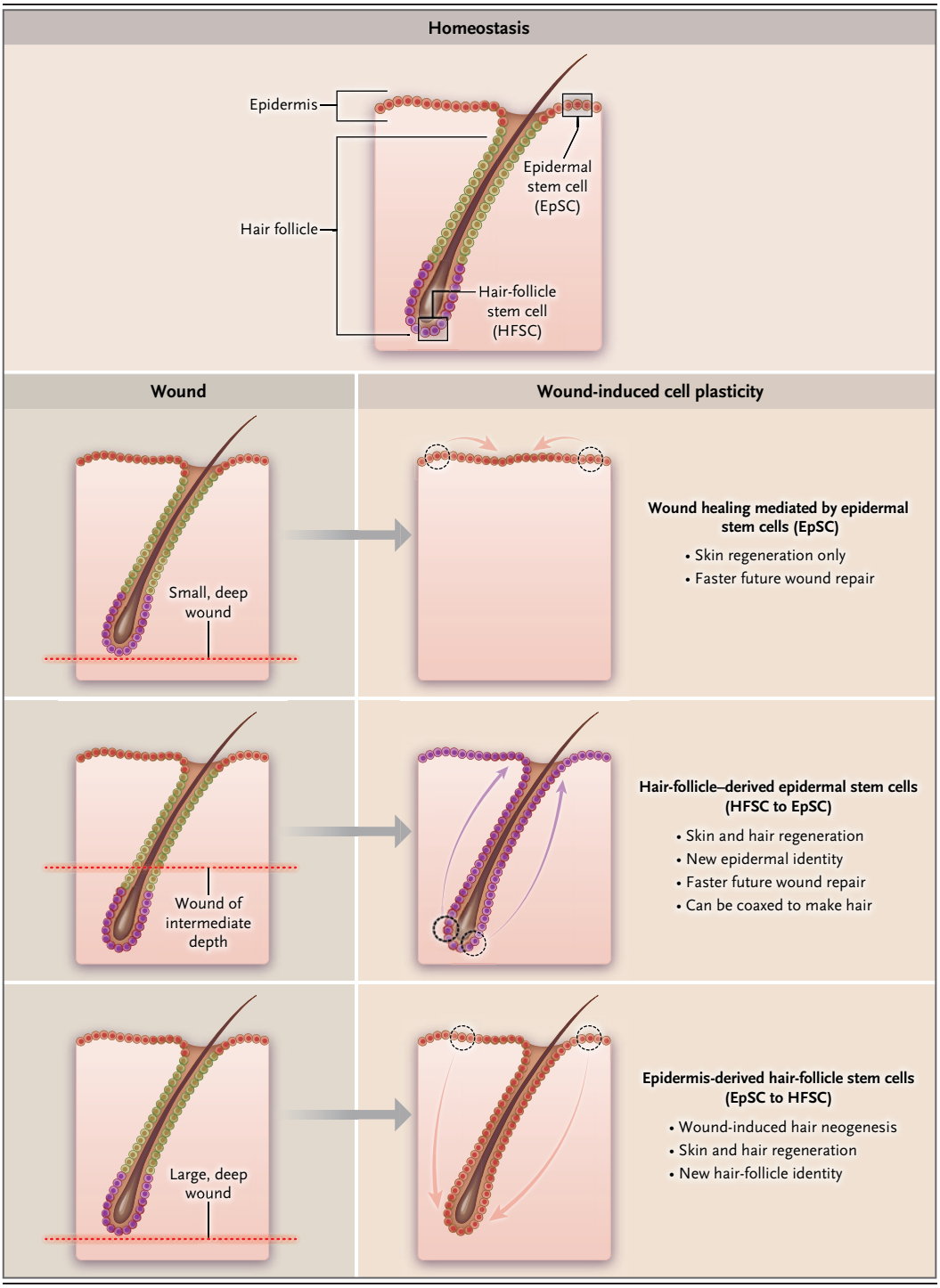
Cellular "memory" — the hallmark ability of immune cells to respond rapidly to previously encountered pathogens — is exhibited by skin cells, which, after exposure to an inflammatory stimulus, respond more quickly and robustly when presented with a second, unrelated stimulus.[1] A recent report by Gonzales et al.[2] describes the way in which skin cells encode multiple memories of their previous identity and experiences. These investigators found that, unlike immune cells, which generate memories by permanently rearranging their DNA, skin cells generate memories through epigenetic changes that are associated with an augmented capacity for regeneration and healing.

The epidermis and hair are continuously produced by separate progenitor-cell populations at the base of their epithelia. Hair follicles also contain a distinct stem-cell population, located in an area called the bulge, that is responsible for cyclically producing new hair. Under homeostatic conditions, epidermal and hair-follicle progenitor cells do not comingle (Fig. 1, top panel). However, in response to wounding, these two stem-cell populations mobilize to close the wound and form new skin.[3]

In a mouse model, Gonzales et al. tracked cells after wounding at various depths to study cell types that heal the skin. Small, deep wounds, which result in removal of the hair follicle, were found to repopulate primarily from cells in the surrounding epidermis, whereas wounds of intermediate depth repopulated from cells in the hair follicle (Fig. 1). Healed skin that was derived from adjacent epidermal cells was indistinguishable from that derived from hair-follicle cells with respect to function and gene expression. Hair-follicle–derived cells essentially assumed a new epidermal identity, but a detailed analysis involving advanced molecular techniques uncovered differences in their DNA organization. In hair-follicle–derived epidermal stem cells, specific areas of DNA were made more accessible through open chromatin; thus, the pattern of DNA accessibility depended on the origin of the cell as well as whether the cell had responded to wounding. For example, cells that had previously responded to wounding had open chromatin regions that coincided with genes that are expressed in response to inflammation and with genes that potentiate the migration of epithelial cells during wound healing (such as the alpha 5 integrin subunit and fibroblast growth factor 2). These new open chromatin regions in previously wounded skin stem cells provided functional advantages for future insults (Fig. 2). New wounds to previously wounded skin stem cells induced earlier changes in gene expression and resulted in swifter cell migration than did wounds to naive stem cells. Ultimately, new wounds to previously wounded skin healed faster than those to naive skin.

Although the conversion of hair-follicle stem cells into epidermis is important for wound healing, the conversion of epidermal cells into hair follicles introduces the intriguing notion of treating hair loss with this approach. Wound-induced hair neogenesis occurs when adult epidermal cells outside the hair-follicle bulge migrate to the center of the wound and generate new hair follicles under the influence of factors secreted by immune cells and dermal cells (Fig. 1).[4] Although Gonzales et al. did not examine wound-induced hair neogenesis specifically, they found that skin derived from hair-follicle stem cells was more likely to form hair follicles than skin derived from naive epidermal cells when transplanted into an inductive environment. A similar



phenomenon occurs in induced pluripotent stem cells, which are biased toward differentiating into their original cell type. Leveraging this understanding may lead to cell-based treatments for hair loss by stimulating specific cell populations with the appropriate signals.

Figure 1 (facing page). Skin Stem Cells and Wound-Induced Cell Plasticity.

During homeostasis, EpSCs and HFSCs separately maintain skin-barrier function and hair production, respectively (top panel). After wounding occurs, both populations of cells contribute to wound healing. Recently, Gonzales et al. found that the type of wound determines which population of stem cells contributes most robustly to healing. Small, deep wounds were found to repopulate from EpSCs and to heal with regeneration of skin only. Wounds of intermediate depth were found to repopulate from HFSCs and to heal with regeneration of skin and hair. Large, deep wounds, which exhibit wound-induced hair neogenesis, are repopulated from EpSCs and heal with regeneration of skin and hair.[4]

The observation that skin from previously wounded or inflamed areas in mice was primed for faster wound healing provides a second translational opportunity. Chronic nonhealing skin wounds, including diabetic foot ulcers, pressure ulcers, and venous ulcers, are as prevalent as heart failure and affect more than 6 million people annually in the United States. Depending on the type of ulcer, conventional treatments include surgical débridement, off-loading, and support stockings. New treatments are sorely needed. The results of the current study raise the possibility of pretreating areas that are prone to ulcers in a manner that creates a "wound memory." Previous research has shown that imiquimod cream, which induces inflammation and is already used in clinical practice to treat precancerous lesions, may be effective in serving this function and can improve wound healing in mice.[1,5] However, translational and clinical studies are needed before these approaches can be considered for the experimental treatment of hair loss and chronic wounds in humans.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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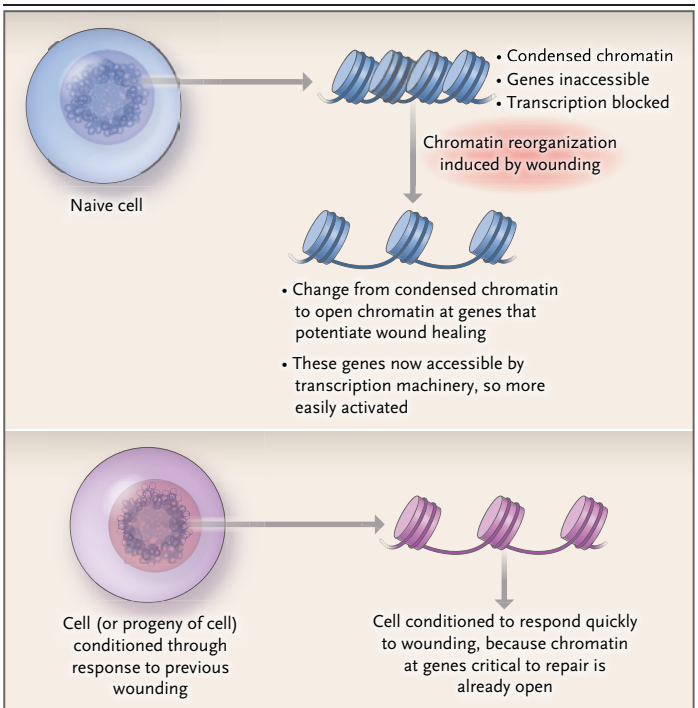

Figure 2. Wound-Induced Epigenetic Cellular Memory.

The chromatin of naive skin stem cells is organized in a specific and precise pattern. Wounds of both intermediate and deep depth result in changes to chromatin, including shifts from condensed to open chromatin around genes that potentiate healing. Cells that participated in a previous healing event maintain the modified chromatin pattern. Thus, genes that potentiate healing are primed for activation when future wounding occurs.

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DOI: 10.1056/NEJMcibr2118516