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Fibroblasts become fat to reduce scarring:

Pathologic scarring could be avoided by manipulating fibroblast plasticity

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Following cutaneous injury in adult mammals, one of two outcomes can occur: successful healing with scar formation or unsuccessful healing and a chronic wound. In humans, scar formation can be classified in terms of “normal scar” formation versus pathologically increased fibrosis, as seen in hypertrophic scarring and keloids (1). Although scarring does not look or function like surrounding unwounded skin, it allows one to survive injury (and hence, procreate). However, extensive scarring from burns and conditions such as scleroderma or epidermolysis bulosa are not only unsightly but also contribute to substantial morbidity owing to loss of functionality in affected tissues and limbs. In the United States alone, there are greater than 50 million incisions and lacerations each year, all of which heal with some degree of scarring (2). Thus, scarring represents an enormous and growing medical burden in our aging population. On page 748 of this issue, Plikus *et al.* (3) demonstrate that scarring could be mitigated by controlling fibroblast plasticity. This has very exciting translational implications for treating scar formation during wound repair.

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A wound represents a complex physiological niche with numerous cell types, cytokines, and growth factors, as well as low oxygen, and high lactate (4). Traditionally, wound repair is thought to proceed through three phases: inflammatory, proliferative, and remodeling (1). The initial inflammatory phase prevents blood loss and infection and clears debris, while the following proliferative phase supports the proliferation and migration of keratinocytes to reseal the epithelium. During the latter remodeling phase, adipocytes, fibroblasts, and extracellular matrix fill the wounded area to form scars. But scars are distinguished from adjacent normal skin by color, texture, and a lack of hair follicles and secondary elements such as sweat and sebaceous glands. Unexpectedly, it was recently found that hair follicle regeneration in mouse wounds could be stimulated with secreted factors of the fibroblast growth factor (FGF) and Wntless (WNT) signaling pathways (5). Plikus *et al.* now make the important finding that hair follicles can change the fate of myofibroblasts (a known cellular player in scarring) into adipocytes through a signaling pathway that depends on bone morphogenetic protein (BMP). Therefore, combinatorial WNT, FGF, and BMP

treatment could present a biphasic strategy for scarless wound healing by first stimulating regrowth of hair follicles that would then induce differentiation of scar-forming myofibroblasts into adipocytes (see the figure). Intriguingly, the authors found that myofibroblasts isolated from keloid patients also could be induced to become adipocytes by exposure to BMP. This has important implications clinically and suggests a potentially effective treatment route for keloids, which are specific to humans and represent pathologic scars that are notoriously difficult to treat because they never stop “growing” and frequently recur even after surgical removal. With these results, Plikus *et al.* illustrate how a better understanding of the complex microenvironment of wounds and the functional plasticity of the cell lineages that contribute to wound repair, could lead to therapies for the physically scarred.

Given the many cell types and signaling pathways involved in wound healing, the reprogramming of a myofibroblast into an adipocyte may not immediately seem surprising because both cell types are classified as mesodermal lineages. For instance, it also has been observed that adipose-resident cell lineages could be converted to skeletal stem cells and skeletal cell lineages through BMP signaling (6). However, recent studies point to tremendous functional heterogeneity in fibroblast and adipocyte cell lineages (7–9). Therefore, it is important to consider the role that fibroblast diversity may play alongside interpretations of fibroblast plasticity.

What is the basis of fibroblast heterogeneity? Both cell-intrinsic and extrinsic factors seem to apply. Known determinants of intrinsic functional diversity in fibroblasts include their ontogeny in a particular fibroblast stem cell-progenitor cell lineage, their tissue of origin (such as skin, lung, or bone), their positional identity (dorsal, ventral, anterior, posterior), and the developmental stage (fetal, adult, aged) of the organism (7–9). Additionally, differences due to variations in extrinsic signaling are important for specifying fibroblast fates (10). Not only is there tremendous diversity in the various tissue microenvironments that contain fibroblasts, but as Plikus *et al.* show, these niches can change dramatically during injury and disease. Fibroblasts in tissues such as vessels, tendons, and skin are normally tasked with forming the connective layers of cells and extracellular matrices that hold soft tissues together. However, injuries disrupt this normal signaling arrangement and expose fibroblasts within the wound niche to infiltrating hematopoietic cell lineages, such as macrophages, and to inflammatory cytokines that can modify their activity. In addition,

Plikus *et al.* show that fibroblasts can respond to BMP that is released by nonhematopoietic epidermal lineages in regenerating cutaneous wounds. It is also possible that fibroblast migration triggered by injury exposes fibroblasts to new sources of signals that they are normally not subjected to, which could be conducive to fibroblast plasticity (10).

What is the true extent of fibroblast plasticity and how does it relate to wound regeneration? Due to the great number of mitigating factors, single-cell approaches are indispensable for deconvoluting the complexities that involve both the intrinsic and extrinsic determinants of fibroblast fates. Genetic tools can enable clonal tracing of single differentiating fibroblast lineages in an animal model to evaluate the frequency of multipotent lineage commitment in the normal setting and upon injury. For example, “Rainbow” and “Confetti” mice are genetically engineered to allow the fluorescent labeling and distinction of individual and adjacent cells. Barcoding techniques can also enable clonal tracing of single differentiating fibroblast lineages in situ (11, 12). Because distinct fibroblast lineages arising from different developmental origins can colocalize to the same tissue, it may be necessary to use newer versions of genetic drivers such as “split-Cre” systems that are triggered by simultaneous activation of two specific promoters rather than one (13). Intravital imaging used in conjunction with clonal-lineage tracing systems could provide powerful evidence for fibroblast plasticity while also tracking other cells in the injury’s microenvironment, including infiltrating macrophages and migrating fibroblasts (14). Prospective isolation techniques could then be employed to isolate the specific fibroblast or fibroblast stem cells in keloids, for example, for functional and single cell molecular characterization so as to determine the mechanistic basis of plasticity (6).

The findings of Plikus *et al.* have broad ramifications for the clinical treatment of fibrotic disorders, including scarring, organ fibrosis (such as lung, liver, or kidney), visceral adhesions, scleroderma, myelofibrosis, and perhaps even aging by suggesting that fibrotic lesions could be transformed into a more innocuous tissue type such as fat if they cannot be removed or prevented from forming directly. At the same time, their results also touch on key questions underlying mesodermal tissue plasticity with important implications for a broad array of topics ranging from mechanisms of cellular reprogramming, as in induced pluripotent stem cells and the epithelial-mesenchymal transition, to the identity of adult mesodermal stem cells and the plasticity of mesodermal populations, including myofibroblasts (15).

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