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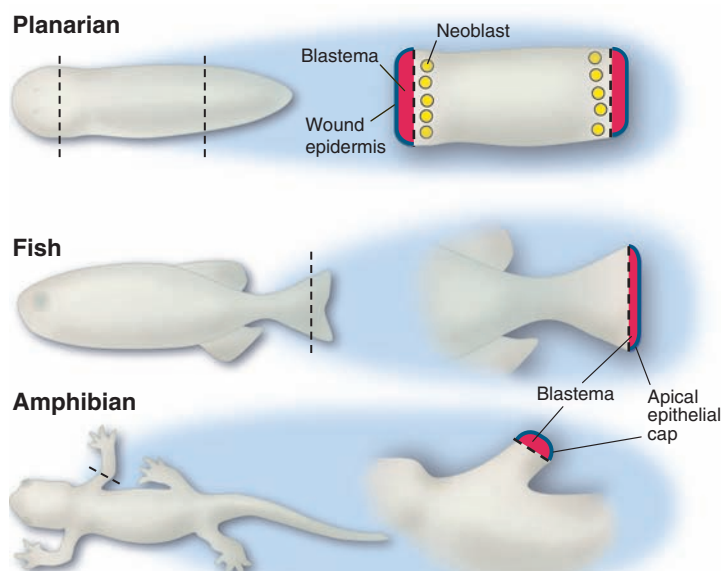
# The Role of Stromal Stem Cells in Tissue Regeneration and Wound Repair

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The process of wound repair in epithelium-lined organs of mammals is complex and is influenced by numerous secreted factors including cytokines, growth factors, and chemokines. However, the cellular organizers of this process are still not understood. Recent studies of tissue regeneration in organisms with simpler development have uncovered details about the activity of stem cells in the mesenchyme (the blastema) during this process. These blastemal cells are well positioned to interpret cues from the environment and to execute decisions about the direction of wound repair. In mammalian wounds, stromal stem cells appear to be positioned to perform functions similar to those of blastemal cells, including communication with both the overlying epithelium and the inflammatory cells in the mesenchyme.

Nearly two millennia ago, Aulus Cornelius Celsus (1) was apparently the first to characterize how human tissue responds to injury, using the terms tumor, rubor, calor, and dolor (swelling, redness, heat, and pain). Since that time, our understanding of the process of the acute response to wounding has become increasingly more sophisticated, and our current level of understanding has been detailed in many excellent textbooks on pathology [e.g., (2)]. Briefly, in this acute phase, soluble mediators are released in the wound and act on (i) the local vascular system to increase permeability and vasodilation; (ii) leukocytes (in particular, neutrophils) to stimulate their chemotaxis into the wound bed; (iii) platelets to aggregate during clotting; and (iv) microbes in order to tag them for removal by macrophages through a process called opsonization. This initial phase is critical to stabilize the wound and allow for a second phase of regenerative activity to occur.

The regenerative phase of wound repair is characterized by the presence of fibroblasts, new blood vessels (created through a process of angiogenesis), and chronic inflammatory cells (consisting predominantly of macrophages) in the wound bed. Understanding the precise role of each cell type in this process is currently an



**Fig. 1.** Regeneration after transection in various model organisms requires specific stem cells in the mesenchyme. Planarians (head or tail), fish (fin), and amphibians (limbs) show regeneration after transection of specific sites. In all cases, a blastema (red) forms at the site of injury. In planarians, the blastema consists of neoblasts; in fish and amphibians, it consists of cells that have undergone dedifferentiation.

intense area of investigation (3–5). One goal of this research is to promote the ideal outcome of wound repair, whereby damaged or lost specialized cells are replaced by cells with functional characteristics and organization similar to those represented before injury. In cases when a chronic damaging stimulus or infection is present, less than satisfactory outcomes of wound repair occur, including altered tissue organization, fibrosis or scarring, and metaplasia (replacement of cellular elements with inappropriate alternative cellular elements), all of which can affect normal function. One method to make wound repair more efficient and minimize undesirable outcomes would be to manip-

ulate the cell type(s) that control this overall process. Stromal stem cells in the wound bed may fulfill this requirement if they can both mediate regeneration and coordinate their actions with the immune system to promote efficient wound repair while preventing infection of the wound bed.

The interplay of stromal stem cells and the immune system is most obvious in epithelium-lined organs that expose the host vascular and immune cells to the environment during injury. The skin and the cornea have emerged as useful systems for study because they are easily accessible and their healing can be observed in a longitudinal manner. Removal or damage of focal areas of skin is typically performed using a punch or incisional biopsy (5); the cornea can be focally damaged by both chemical and physical means (6, 7). Other epithelium-lined organs that are amenable to damage and study of wound repair include mucosa-lined structures such as the lung and gut, which offer unique challenges and perspectives concerning this process. Because the key function of both the lung and gut is the physiologic exchange of either gas or nutrients with the environment, only a single layer of epithelial cells is present to act as a barrier to a numerous and diverse group of microbes [e.g., (8) for the intestine]. This epithelium can be damaged experimentally by well-defined chemical or physical means (9–11). A variety of studies have detailed the secreted factors that influence wound healing, identifying well-known families of growth factors such as epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor- $\beta$  (TGF- $\beta$ ), and vascular endothelial growth factor (VEGF). Various other hormones, growth factors, cytokines, and chemokines also influence wound repair (12).

Our knowledge of how this myriad of secreted factors is coordinated at the cellular level during injury repair remains incomplete. Much attention has been placed on the definition and behavior of epithelial stem cells that are responsible for the maintenance of this part of the barrier. However, it is not completely clear how mesenchymal elements are organized and regenerated in wound repair and to what extent they play a role in the proper regeneration of the epithelium. One reason why this has been difficult to discern is that injury sites in mice and humans typically contain a

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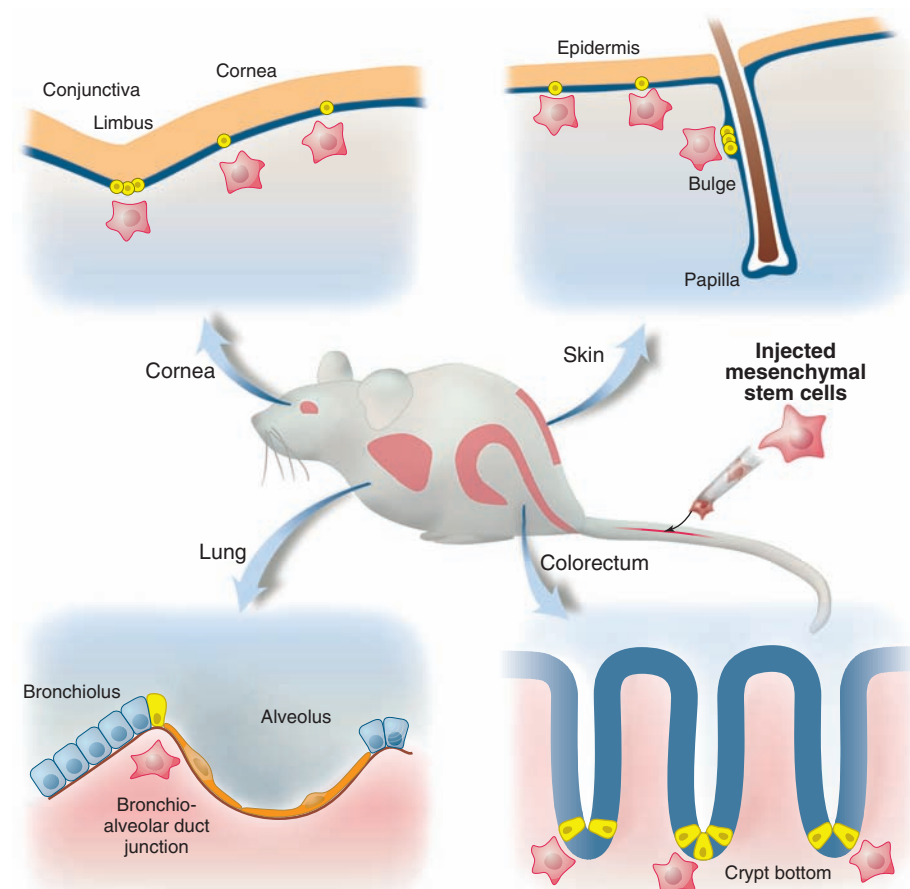
robust inflammatory infiltrate that is intermingled with these mesenchymal cells. The thesis of this review is that lessons from the study of tissue regeneration in simpler developmental systems that point to undifferentiated mesenchymal elements as the key to this process will be instructive for investigators studying mammalian repair. These undifferentiated mesenchymal cells in simpler organisms are similar to mammalian mesenchymal stem cells (MSCs) (13) that are currently being studied in experimental models of injury and are being used to treat a growing number of chronic diseases in which wound repair is deficient (14). The more primitive mesenchymal cells may also be in a position in the wound bed to communicate with the immune system to ensure an appropriate level of inflammation.

### Lessons from Regeneration in Model Organisms

In its simplest form, regeneration can be performed by resident, totipotent stem cells that normally maintain homeostasis by replenishing cells lost to turnover. Many simple organisms such as planarians, hydra, and starfish use this strategy for large-scale regeneration of substantial portions of their body plan after resection (15) (Fig. 1). The planarian *Schmidtea mediterranea* offers experimental advantages because its genome has been sequenced and RNA interference can be used to study gene functions (16, 17). The planarian stem cell, the neoblast, is radiation-sensitive and is solely responsible for regeneration after resection (18, 19). After resection of either the head or the tail of the planarian, neoblasts respond by proliferation and migration to the site of the injury, where in aggregate they form a blastema (a structure composed of undifferentiated cells). The blastema is the nidus for the formation of all the excised structures in a given region of the planarian, including the ectoderm, rudimentary gut, and reproductive system.

Analysis of mRNA microarray profiles of planarian neoblasts showed that >75% of their enriched mRNAs (with known mammalian homologs) could be classified into categories of protein biosynthesis, RNA binding, transcription, and DNA binding (20). All four of these categories represent intracellular processes that have been shown to be enriched in a variety of stem cells isolated from both mouse and human organs and embryos (21).

Even in this simplest case, neoblasts in transected planarians require instructive cues so that regeneration proceeds correctly. During regeneration, **loss of Wnt signaling affects the anteroposterior axis recognition**. Treatment of planarians with small interfering RNAs that abrogate Wnt signaling after tail resection results in a spectacular phenotype of a second "head" that is regenerated in place of the tail (22–24). The specification of an anteroposte-



**Fig. 2.** Injected mesenchymal stem cells (MSCs) home to various sites of injury in mice. MSCs injected into the vascular system can home to various epithelium-lined organs including lung, gut, skin, and cornea (red). Corneal and skin epithelium contain multiple layers (orange, superficial; blue, basal layer). Stem cells are yellow and are present in the limbus of the cornea and hair follicle bulge of skin, although these cells also appear to be located in the cornea away from the limbus and in the interfollicular areas of skin as well in the basal layer. The lung and gut epithelium are single cell layers. The lung epithelium transitions from cuboidal-shaped cells to flat cells (blue and orange, respectively). The stem cell (yellow) may be located at the junction of these cell types. The colonic epithelium contains a layer of tall columnar-shaped cells (blue). The colonic stem cells (yellow) are located at the base of invaginations of this epithelium called crypts of Lieberkühn. In all cases, MSCs migrate to the mesenchyme of injured organs. Their as yet unproven interaction with stem cells in each organ is depicted.

rior axis during regeneration also appears to require Wnt signaling in another model system, the hydra (25). Loss of bone morphogenetic protein (BMP) signaling affects proper mediolateral regeneration that is manifested by a lack of regeneration in this area of the planarian (26, 27). An important emerging lesson from this recent work is that cell position and spatial orientation are critical to shape the activity of stem cells so that their actions are properly coordinated with the needs of the organism. Additional studies in this experimental system that determine the source of Wnt and BMP signals, as well as the cells that respond to them, will likely provide new ideas about how stem cells can shape regeneration.

Regeneration of higher-order organisms requires the coordinated action of multiple stem

cell types. Fish and urodele amphibians (salamanders and newts) have the well-recognized ability to regenerate epithelium-covered appendages that have been amputated (Fig. 1; fins in fish and limbs in amphibians). Both systems are characterized by a phase of cellular dedifferentiation at the wound site, involving both mesenchymal and epithelial elements, that occurs soon after amputation. Epidermal cells dedifferentiate and migrate to close off the wound site from the environment. When this apical epithelial cap forms, undifferentiated cells in the mesenchyme then proliferate to form a blastema, which, as a structure, is morphologically similar to the limb bud in early development (28). Blastemal cells most likely are derived from local, mature dermal cells that dedifferentiate, although there appears to be a contribution of

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dedifferentiated cells from muscle and bone as well (28).

The amphibian limb blastema is exquisitely organized. Transplantation studies during amphibian limb regeneration have shown that the proximal blastema gives rise to the proximal portion of the limb, and the distal blastema likewise gives rise to the distal limb (29). Blastemal cells, although morphologically indistinct, seem to be functionally distinct, programmed to know where they are placed in an organism or wound. Blastemal cells are “proximalized” by retinoic acid, which induces the expression of Meis homeobox domain proteins (30). This concept appears to have application in adult mammalian organs as well. A similarly seemingly indistinct cell type, the stromal fibroblast isolated from skin, is provided the equivalent of a “hometown address” simply on the basis of its location in the body. This idea was generated by an array analysis of mRNAs from human mesenchymal fibroblasts isolated from different areas of the body that showed differential expression of specific genes, notably the **Hox family** (31). Furthermore, skin fibroblasts from a single location also contain geographic specificity. Superficial skin fibroblasts (with respect to the organ surface) have distinct properties of growth, collagen gel contraction, and growth factor production relative to skin fibroblasts isolated from deeper within the organ [reviewed in (32)].

In salamander limb regeneration, the blastema requires instructive cues from differentiated cells located nearby. For example, denervated limbs in this system do not regenerate (33), reflecting an interdependence between blastemal stem cells and nearby nerves that depends on a gradient of *Prod1* present on the cell surface of blastemal cells and its ligand, *AG*, which is secreted by Schwann cells that make up the nerve sheath (34). Blastemal proliferation in the regenerating zebrafish fin is also regulated by a number of growth factors including FGFs. MicroRNA-133 levels (normally high in the uninjured fin) are quickly depleted by FGF signaling to promote appendage restoration through the expression of *Mps1* kinase, which stimulates blastemal proliferation (35). MicroRNAs regulate mRNAs (in part by controlling stability) in the progeny of stem cells (36) during development and seemingly during wound repair as well.

## Application to Mammalian Wound Repair

In mice and humans, the scope of tissue regeneration is much more limited. “Limb” regeneration is restricted to the distal tip of digits (28). In mice, this process requires the transcription factor ***Msx1* and BMP signaling** (37). After injury, the epithelium overlying the lost digit tip induces mesenchymal expression of *Msx1*, which stimulates dedifferentiation of a variety of mesenchymal

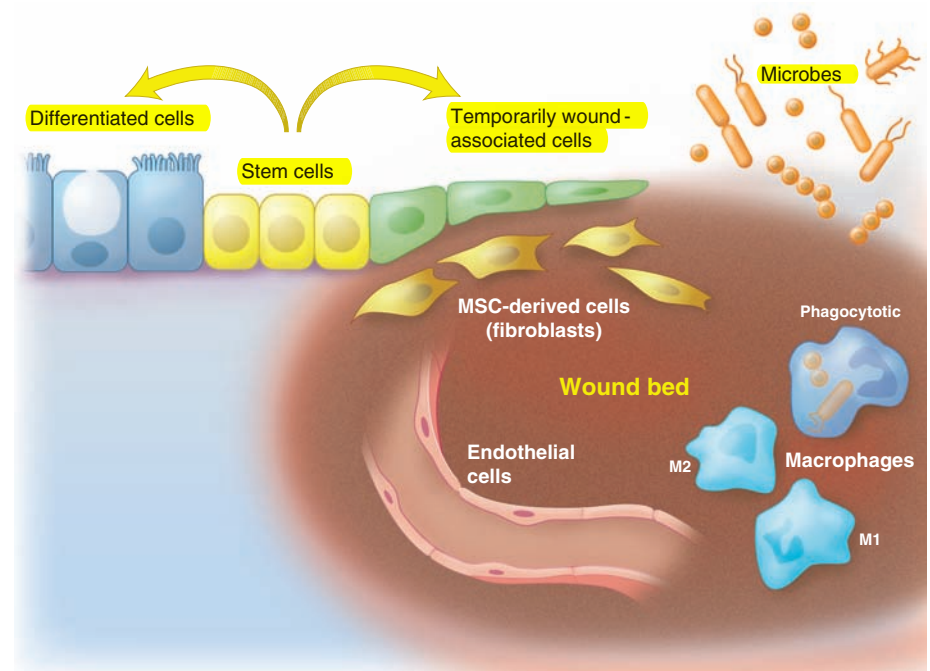
cell types (38). These dedifferentiated mesenchymal cells are an important source of the regeneration in this system. It remains unknown why limb regeneration exists in principle but is in actuality so limited in mice and humans.

In mammals, the concept of regeneration can be extended if one considers the restoration of morphologically distinct epithelial stem cell-containing substructures located within an organ. Examples of such “mini” organs include hair follicles in skin, crypts in the intestine, and the limbus in the cornea. Hair follicle regeneration in response to punch biopsy wounds in skin depends on Wnt signals (39). Like the planarian regeneration system, Wnt signaling is required for the patterning of this “mini” organ during its regeneration (analogous to regeneration of one end of the planarian). However, also like the planarian, the precise cellular source(s) and target(s) of the Wnt signals have not been completely defined. In particular, defining the role of Wnt signaling within the mesenchyme itself will be quite important. Crypts and glands that line the gut are thought to regenerate, in part through a process of crypt fission (40), although the molecular triggers of this process are not yet clear. In the cornea, **loss of Notch function in the epithelium has profound consequences during corneal wound regeneration**, such that the mesenchyme no longer transmits appropriate signals back to

the epithelium, resulting in abnormal epithelial differentiation (41).

A key unanswered question in all of these mammalian organ systems is the cell type that communicates with the epithelium to modulate wound repair. No morphologic blastema has been recognized to form in mammalian wounds. However, injected MSCs may be able to coordinate wound repair. MSCs, initially isolated on the basis of their ability to quickly adhere to tissue culture plastic, can differentiate into multiple mesenchymal lineages depending on available growth factors (14). Many studies have used injection of these cells (derived mostly from bone marrow and fat) to show that they can migrate to a variety of wound sites including the skin, cornea, gut, and lung (42–46) (Fig. 2). The homing of MSCs to certain anatomic locations requires specific glycosylation states of CD44 on the MSCs (47).

Because of the crude method of isolating MSCs, there is substantial interest in determining the cell type or types that they represent. Recently, multiple investigators have proposed that fibroblasts isolated from a variety of tissues appear to have very similar properties to these MSCs, including the ability to differentiate into multiple mesenchymal lineages (48, 49). Thus, MSCs when injected into the bloodstream of a human or mouse may represent a mobilized form of a tissue-



**Fig. 3.** Model of a potential role of tissue-resident fibroblasts in wound repair of epithelium-lined organs. The wound bed consists primarily of fibroblasts, new blood vessels, and macrophages, as labeled. The epithelium consists of stem cells that produce differentiated cells away from the wound bed and produce less differentiated cells that are associated with the wound bed. The timing and balance between wound repair and elimination of microbes in the wound bed must be properly orchestrated. The fibroblast may be in position to mediate this function by communication with overlying epithelial cells and macrophages within the wound bed.

resident fibroblast. Another intriguing proposal is that MSCs are pericytes (50), a supporting cell for blood vessels. This idea raises an intriguing connection between these cells and the microvasculature that undergoes such marked physiologic changes early in healing and must be remodeled in the late stage of healing. Finally, additional organ-resident, multipotent stromal stem cells with overlapping but distinct properties relative to MSCs have been isolated and characterized. An example is skin-derived precursors (SKPs) that are present in the adult and can differentiate not only into mesenchymal lineages but also neural lineages in vitro (51).

The primary function of MSCs in wound repair appears to depend on the site and type of injury. MSCs either can provide daughter cells that differentiate and then directly participate in the structural repair of a wound, or can supply secreted factors that support wound repair and modulate the immune system [e.g., (46, 52, 53)]. It is possible that MSCs, which can be isolated from virtually all tissue types, nonetheless may feature distinctive properties (including the ability to repair wounds) and markers when isolated from different tissues (54, 55). This implies that MSCs may function within a tissue during injury repair, although they have not yet been observed to localize to a particular area of the wound. It is not known whether MSCs “dedifferentiate” during injury repair, or whether they simply divide and increase their representation in the wound bed. In any case, these cells may be strategically placed to communicate with overlying epithelial stem cells and the remainder of the wound-associated mesenchyme. To test this idea, it will be critical to develop novel tools to perform lineage-tracing studies of tissue-specific stromal cells as well as to knock out genes within them.

One cell type with which MSCs communicate under a variety of circumstances is macrophages (Fig. 3). Macrophages are often a dominant cell type in the mature wound bed and perform the critical function of killing and clearing any invading microbes. MSCs can secrete factors such as prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) that down-modulate inflammatory cytokines that are produced by macrophages in response to encounters with microbes (56, 57). Interestingly, PGE<sub>2</sub> can also potentiate Wnt signaling during repair in various organs (58), thus potentially linking immune and stem cell modulation. It is not clear whether the communication of MSCs (or any other cell type, for that matter) can program macrophages so that they aid in wound repair, as first suggested by Ross and colleagues in 1975 (59). This idea has led to the proposal that alternatively activated macrophages (through stimulation with interleukins IL-4 and IL-13) secrete factors that promote wound repair, whereas conventionally activated macrophages secrete a variety of pro-

inflammatory cytokines that can inhibit wound repair (60). In support of this idea, Trem-2 knockout mice showed diminished expression of markers of alternatively activated macrophages in the wound bed of biopsy-injured mouse colons and showed diminished ability to heal wounds (11). However, the key test of this idea is to study mice that lack tissue-resident macrophages. In support of a positive role for macrophages in the response to tissue injury, colonic epithelial progenitors showed cell cycle arrest in *Csf1<sup>op/op</sup>* mice (which lack macrophages in many organs, including the gut) when injured with dextran sodium sulfate (61). Evidence that does not support a positive role of macrophages in injury repair comes from the study of skin injury using *PU.1<sup>-/-</sup>* mice [which also lack macrophages (62)]. Additional studies will obviously be required to further understand the role of macrophages and MSC-macrophage interactions in wound repair.

Understanding the mechanisms that underlie normal wound repair is of profound medical importance, because many disease states include elements of nonhealing or poorly healing lesions. Given the role of MSCs in wound repair of developmental systems and their emerging use as therapeutic agents, we propose that MSCs may be a critical, manipulable component of wound repair in humans. Understanding the role of MSCs within the tissue where a wound occurs will be quite valuable. What we lack are methods to specifically mark and trace the lineage of resident MSCs. Such methods, when developed, will help us to determine the extent to which MSCs act as stem cells or as sources of secreted factors, as well as to dissect this cell type into distinct and functional subpopulations.

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