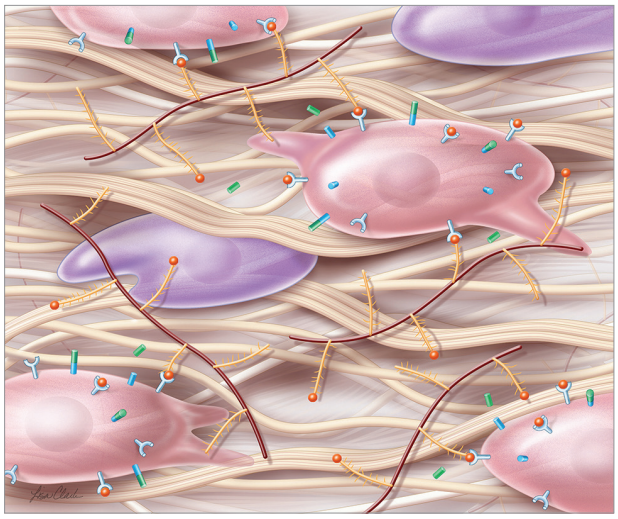
Dynamic reciprocity and wound healing

Dynamic reciprocity

Normal wound healing is characterized by a well-coordinated, progressive series of events designed to restore the barrier function and mechanical integrity of the skin. It involves interactions between cells and their microenvironment, of which the extracellular matrix (ECM) is the primary component. It is through these interactions that cells are directed to differentiate or dedifferentiate, proliferate or remain quiescent, and assume the architecture and function of the skin.[1]

Figure 1



Cells directly interact with their local ECM environment in a process called "dynamic reciprocity."

This direct ECM/cell interaction is a process that has been termed "dynamic reciprocity" (Figure 1).[2] In a natural environment void of injury, the ECM and the cells communicate with each other and respond dynamically to each other to maintain homeostasis. After injury occurs and the ECM is damaged, cells need to restore the local tissue structure by removing the debris from the damaged ECM and replacing it with healthy ECM, ultimately achieving tissue restoration via the process of constructive tissue remodeling.[3]

Dynamic reciprocity and normal wound healing

The stages of normal wound healing include initial hemostasis, characterized by clot formation; inflammation, characterized by the deposition of inflammatory and progenitor cells, leading to the removal of bacteria and devitalized tissue; proliferation, where resident cells secrete growth factors and cytokines and collagen deposition occurs to rebuild the ECM, resulting in granulation tissue formation; and remodeling, where the newly formed tissue matures and collagen strength increases to meet the demands of the body.[4]

Dynamic reciprocity is an essential mechanism by which the well-coordinated, progressive series of events of wound healing occurs. Examples can be found in each stage. During hemostasis, the direct interaction between platelets and the exposed ECM collagen triggers a series of events that leads to eventual thrombus formation and the stabilization of the fibrin clot.[5] During inflammation, monocytes bind to fibronectin, which increases their phagocytic capacity and leads to increased breakdown of damaged ECM and removal of cellular debris—essential steps if wound healing is going to proceed to the proliferation stage.[6] During the proliferation stage of wound healing, fibroblast binding to fibronectin stimulates their secretion of matrix-degrading enzymes, which in turn enhances endothelial cell migration and blood vessel formation (angiogenesis).[7] As angiogenesis progresses, endothelial cells form tubes, which involves the recruitment of pericytes in response to endothelial cell-derived basic fibroblast growth factor (FGF-2) and platelet-derived growth factor (PDGF).[8] Finally, as an example of dynamic reciprocity in the remodeling stage of wound healing, fibroblasts bound to fibronectin through

integrin receptors migrate and proliferate in response to PDGF.[9] When this interaction occurs in the presence of TGF-β1, the fibroblasts are directed to preferentially secrete collagen type I instead of collagen type III, and a fraction of them are instructed to differentiate into myofibroblasts.[10] Myofibroblasts are then able to interact with collagens in the ECM to stabilize and remodel the wound.

The above are only discrete examples of dynamic reciprocity that occur in different stages of wound healing. In reality, each wound healing stage requires the coordinated effects of many different cell types and ECM components to lead the wound through the normal wound healing process.

Dynamic reciprocity and non-healing wounds

While most wounds heal in a timely and orderly pattern, the process can be stalled or stopped completely in patients with diabetes mellitus, venous insufficiency, suppressed immune systems, or following immobility that leads to prolonged pressure. Chronic wounds may develop in these cases, potentially leading to pain, immobility, hospitalization, and/or amputation.

Non-healing wounds fail to exhibit the normal sequence of actions and reactions between cells and the ECM that characterizes acute wound healing because of changes in the physiological environment resulting from the underlying disease. The normal, sequential pattern of these interactions does not occur, and the disruption of these interactions leads to downstream effects on other cell-ECM interactions that ultimately delay or prevent healing.[1]

Disease-related abnormalities that lead to the occurrence of chronic wounds include changes in cellular responsiveness, elevated proteolytic environments, and microvascular abnormalities. For example, diabetes is associated with deficits in the bactericidal action of granulocytes,[11] glycation of collagen and fibronectin that interferes with epithelial cell adherence,[12] and a decreased vasodilatory response.[13] Chronic wounds are characterized by the presence of elevated levels of various metalloproteases (MMPs) and decreased levels of tissue inhibitors of metalloproteases (TIMPs);[14] studies have found a correlation between elevated MMP levels, chronic inflammation, and non-healing wounds.[15,16]

Excessive degradation of the ECM and growth factors by MMPs deprives cells of attachment sites and signals required for migration, differentiation, and proliferation. The result is that cells can no longer respond to the normal cues in their environment, thus preventing the sequential series of changes in the matrix composition needed for wound healing to progress.[1]

Harnessing dynamic reciprocity to achieve healing

The presence of a natural, intact ECM in the local wound environment is essential for successful wound healing.

Restoring the natural ECM environment using tissue-engineered products has been shown to be an effective treatment strategy for a wide variety of acute and chronic wounds.[3] These materials can positively alter the local environment and lead to constructive tissue remodeling.[3,17,18] Due to dynamic reciprocity, the patient's cells remodel the biomaterial into the patient's own local tissue with local tissue properties. Rather than relying on the patient's cells to generate their own ECM or ECM attachment sites in a suboptimal healing environment, direct application of intact ECM may be an effective strategy for optimizing wound healing outcomes and improving patients' quality of life.

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