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Wound Healing/Repair and Regeneration in Periodontal Tissues

Dr. Anjali Kothari

MDS Dept of Periodontics, PGIDS, Rohtak

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WOUND HEALING

Wound healing is a complex but generally orderly process. Sequential waves of specialized cell types first clear the inciting injury and then progressively build the scaffolding to fill in any resulting defect. The events are orchestrated by interplay of soluble growth factors and ECM; physical factors, including the forces generated by changes in cell shape, also contribute. Wound healing may ultimately be reduced to a sequence of processes that we have previously discussed:

- Induction of an acute inflammatory response by the initial injury
- Parenchymal cell regeneration (where possible)
- Migration and proliferation of both parenchymal and connective tissue cells
- Synthesis of ECM proteins
- Remodeling of parenchymal elementsto restore tissue function
- Remodeling of connective tissue to achieve wound strength

Here, we specifically describe the healing of skin wounds. This is a process involving both epithelial and connective tissue regeneration.

Healing by First Intention

One of the simplest examples of wound repair is the healing of a clean, uninfected surgical incision approximated by surgical sutures. This is referred to as *primary union* or *healing by first intention.* The incision causes only focal disruption of epithelial basement membrane continuity and death of a relatively few epithelial and connective tissue cells. As a result, epithelial regeneration predominates over fibrosis. The narrow incisional space rapidly fills with fibrin-clotted blood; dehydration at the surface produces a scab to cover and protect the healing repair site.

Within 24 hours, neutrophils are seen at the incision margin, migrating toward the fibrin clot. Basal cells at the cut edge of the epidermis begin to exhibit increased mitotic activity. Within 24 to 48 hours, epithelial cells from both edges have begun to migrate and proliferate along the dermis, depositing basement membrane components as they progress. The cells meet in the midline beneath the surface scab, yielding a thin but continuous epithelial layer.

By day 3, neutrophils have been largely replaced by macrophages, and granulation tissue progressively invades the incision space. Collagen fibers are now evident at the incision margins, but these are vertically oriented and do not bridge the incision. Epithelial cell proliferation continues, yielding a thickened epidermal covering layer.

By day 5, neovascularization reaches its peak as granulation tissue fills the incisional space. Collagen fibrils become more abundant and begin to bridge the incision.

Surface cells yield a mature epidermal architecture with surface keratinization.

During the second week, there is continued collagen accumulation and fibroblast proliferation. The leukocyte infiltrate, edema, and increased vascularity are substantially diminished. The long process of "blanching" begins, accomplished by increasing collagen deposition within the incisional scar and the regression of vascular channels.

By the end of the first month, the scar comprises a cellular connective tissue largely devoid of inflammatory cells and covered by an essentially normal epidermis. However, the dermal appendages destroyed in the line of the incision are permanently lost. The tensile strength of the wound increases with time, as described later

Healing by Second Intention

When cell or tissue loss is more extensive, as in infarction, inflammatory ulceration, abscess formation, or even just large wounds, the reparative process is more complex. In these situations, regeneration of parenchyma cells alone cannot restore the original architecture. As a result, there is extensive ingrowth of granulation tissue from the wound margin, followed in time by accumulation of ECM and scarring. This form of healing is referred to as *secondary union,* or *healing by secondary intention.*

Secondary healing differs from primary healing in several respects:

Large tissue defects intrinsically have a greater volume of necrotic debris, exudate, and fibrin that must be removed. Consequently, the inflammatory reaction is more intense, with greater potential for secondary, inflammation-mediated, injury.

Much larger amounts of granulation tissue are formed. Larger defects accrue a greater volume of granulation tissue to fill in the gaps in the stromal architecture and provide the underlying framework for the regrowth of tissue epithelium. A greater volume of granulation tissue generally results in a greater mass of scar tissue. Secondary healing exhibits the phenomenon of *wound contraction.* Within 6 weeks, for example, large skin defects may be reduced to 5% to 10% of their original size, largely by contraction. This process has been ascribed to the presence of *myofibroblasts,* modified fibroblasts exhibiting many of the ultrastructural and functional features of contractile smooth muscle cells.

Wound Strength

Carefully sutured wounds have approximately 70% of the strength of unwounded skin, largely because of the placement of the sutures. When sutures are removed, usually at 1 week, wound strength is approximately 10% of that of unwounded skin, but this increases rapidly over the next 4 weeks. The recovery of tensile strength results from collagen synthesis exceeding degradation during the first 2 months, and from structural modifications of collagen (e.g., cross-linking and increased fiber size) when synthesis declines at later times. Wound strength reaches approximately 70% to 80% of normal by 3 months but usually does not substantially improve beyond that point.

GENERAL ASPECTS OF WOUND HEALING / REPAIR AND REGERATION

Extracellular Matrix and Cell-Matrix Interactions

ECM is *a dynamic, constantly remodeling*macromolecule complex synthesized locally and constituting a significant proportion of any tissue. Besides providing turgor to sr tissues and rigidity to Done, ECM supplies a substratum for cell adhesion and critically regulates the growth, movement and differentiation of the cells living within it. ECM occurs in two basic forms: *interstitial matrix* and *basement membrane (BM).*

Components of the Extracellular Matrix

There are three basic components of ECM: fibrous structural proteins that confer tensile strength and recoil, water-hydrated gels that permit resilience and lubrication, and adhesive glycoproteins that connect the matrix elements one to another and to cells

Collagen. The *collagens* are fibrous structural proteins conferring tensile strength. These proteins are composed of three separate peptide chains braided into a ropelike triple helix; the individual chains are able to tightly intertwine because the peptide chains have glycines present at every third position. Mutations changing the glycines to other amino acids, or any other abnormalities leading to poor collagen braiding, result in defective ECM synthesis with catastrophic consequences to bone, skin, aorta, and other tissues. More than 30 distinct peptide chains form approximately 18 different collagen types, some of which are unique to specific cells and tissues. The fibrillar collagens form a major proportion of the connective tissue in healing wounds and particularly in scars.

Elastin. Although tensile strength is derived from the fibrillar collagens, the ability of tissues to recoil and return to a baseline structure after physical stress is conferred by elastic tissue. This is especially important in the walls of large vessels (which must accommodate recurrent pulsatile flow), as well as in the uterus, skin, and ligaments. Morphologically, elastic fibers consist of a central core of *elastin* protein, surrounded by a meshlike network of *fibrillin* glycoprotein. Like collagens, elastins require a glycine in every third position, but they differ from collagen by having fewer cross-links. The fibrillin meshwork serves as a scaffold for the deposition of elastin and assembly of elastic fibers; defects in fibrillin synthesis lead to skeletal abnormalities and weakened aortic walls *(Marfan syndrome*).

Proteoglycans and hyaluronan: These molecules form highly hydrated compressible gels conferring resilience and lubrication (such as in the cartilage in joints). They consist of long polysaccharides called *glycosaminoglycans* (examples are *dermatan sulfate* and *heparan sulfate)* linked to a protein backbone much like bristles on a test tube brush. *Hyaluronan,* a huge molecule composed of multiple disaccharide repeats without a protein core, is also an important constituent of the ECM, principally because of its ability to bind volumes of water into a viscous, gelatin-like matrix. Besides providing compressibility to a tissue, proteoglycans also serve as reservoirs for growth factors secreted into the Pn (e.g., bFGF). Any damage to the ECMfc releases the bound growth factor, which can initiate if healing process. Proteoglycans can also be integral cell membrane proteins and in that capacity modulate eel growth and differentiation. For example, the transmembrane proteoglycan *Syndecan* has attached hyaluronan chains that can bind matrix growth factors like bFGF: this binding facilitates the interactions of bFGF with appropriate cell surface receptors (see Fig. 3-7). *Syndecan* also associates with the intracellular actin cytoskeleton and thereby helps to maintain normal epithelial sW morphology.

Adhesive glycoproteins and integrins. Adhesive glycoproteins are structurally diverse molecules whose major role is to link ECM components to one another and to link ECM to cells via cell surface integrins. The adhesive glycoproteins include (among many) fibronectin (major component of the interstitial ECM) and laminin (major constituent of BM), described here as prototypical of the overall group.

Fibronectin is a large (450-kD) disulfide-linked heterodimer synthesized by a variety of cells, including fibroblasts, monocytes, and endothelium and associated with cell surfaces, BMs, and pericellular matrix. It has specific domains that bind to a wide spectrum of ECM components (e.g., collagen, fibrin, heparin, and proteoglycans) and can also attach to cell integrins via a tripeptide arginine-glycine-aspartic acid (abbreviated ROD) motif. This ROD recognition sequence plays a key role in cell-ECM adhesion.

Laminin is the most abundant glycoprotein in BM; it is an 820-kD cross-shaped heterodimer that connects cells to underlying ECM components such as type IV collagen and heparan sulfate. Besides mediating attachment to BM, laminin also modulates cell survival, proliferation, differentiation, and motility.

Integrins are a family of transmembrane heterodimeric glycoproteins whose intracellular domains associate with cytoskeletal elements (e.g., vinculin and actin at focal adhesion complexes). Integrins on epithelial or mesenchymal cells also bind to ECM via ROD motifs; these interactions signal cell attachment and can affect cell locomotion, proliferation, or differentiation. Integrin-ECM interactions can utilize the same intracellular signaling pathways used by growth factor receptors; for example, integrin-mediated adhesion to fibronectin can trigger elements of the MAP kinase, phosphyrylase 3-kinase and protein kinase c pathways. In this manner, extracellular mechanical forces can be coupled to intracellular synthetic and transcriptional pathways.

Thus, adhesive matrix proteins such as fibronectin and laminin can directly mediate the attachment, spread, and migration of cells. By activating intracellular signaling pathways, fibronectin also enhances the sensitivity of certain cells (e.g., endothelium) to the proliferative effects of growth factors. In the early stages of healing skin wounds, large quantities of plasma-derived fibronectin accumulate in the ECM and act as provisional scaffolding for the ingrowth of endothelium and fibroblasts. After 2 or 3 days, the fibronectin in the healing wound is actively synthesized by proliferating endothelial cells

REPAIR BY CONNECTIVE TISSUE (FIBROSIS)

- Formation of new blood vessels *(angiogenesis)*
- Migration and proliferation of fibroblasts
- Deposition of ECM
- Maturation and reorganization of the fibrous tissue *(remodeling)*

Repair begins within 24 hours of injury by the emigration of fibroblasts and the induction of fibroblast and endothelial cell proliferation. By 3 to 5 days, a specialized type of tissue that is characteristic of healing, called *granulation tissue* is apparent. The term *granulation tissue* derives from the pink, soft, granular gross appearance, such as that seen beneath the scab of a skin wound. Its histologic appearance is characterized by proliferation of fibroblasts and new thin-walled, delicate capillaries, in a loose ECM. Granulation tissue then progressively accumulates connective tissue matrix.

Angiogenesis

Blood vessels are assembled by two processes: *vasculogenesis*, in which the primitive vascular network is assembled from *angioblasts* (endothelial cell precursors) during embryonic development; and *angiogenesis*, or *neovascularization*, by which preexisting vessels send out capillary sprouts to produce new vessels. Angiogenesis is a critical process in the healing at sites of injury, in the development of collateral circulations at sites of ischemia, and in allowing tumors to increase in size beyond the constraints of their original blood supply. Thus, much work has been done in understanding the mechanisms underlying such neovascularization and therapies to either augment the process. Proteolytic degradation of the parent vessel BM allows formation of a capillary sprout migration of endothelial cells from the original capillary toward an angiogenic stimulus.

- Proliferation of the endothelial cells behind the leading edge of migrating cells
- Maturation of endothelial cells with inhibition of growth and organization into capillary tubes; this includes recruitment and proliferation of *pericytes* (for capillaries' and *smooth muscle cells* (for larger vessels) to support the endothelial tube and provide accessory functions

These new vessels are leaky because of incompletely formed interendothelial junctions and increased transcytosis.

Fibrosis

Fibrosis or *scar formation,* builds on the granulation tissue framework of new vessels and loose ECM that develop early at the repair site. The process of fibrosis occurs in two steps: *(1) emigration and proliferation of fibroblasts into the site of injury, and (2) deposition of ECM by these cells.* The recruitment and stimulation of fibroblasts is driven by many of the growth factors described later, *including platelet-derived growth factor (PDGF), bFGF,* and *TGF-a.* One source of these factors is the activated endothelium. However and perhaps more importantly, growth factors are also elaborated by inflammatory cells. Macrophages, in particular, are important cellular constituents of granulation tissue, and besides clearing extracellular debris and fibrin at the site of injury, they elaborate a host of mediators that induce fibroblast proliferation and ECM production. Sites of inflammation are also rich with mast cells, and with the ap-propriate chemotactic milieu, lymphocytes may also be present. Each of these can contribute directly or indirectly to fibroblast proliferation and activation.

As healing progresses, the number of proliferating fibroblasts and new vessels decreases; however, the fibroblasts progressively assume a more synthetic phenotype, and hence there is increased deposition of ECM. Collagen synthesis, in particular, is critical to the development of strength in a healing wound site. As described later, collagen synthesis by fibroblasts begins early in wound healing (days 3 to 5) and continues for several weeks, depending on the size of the wound. Many of the same growth factors that regulate fibroblast proliferation also participate in stimulating ECM synthesis. Collagen synthesis, for example, is induced by a number of the molecules, including growth factors (PDGF, bFGF, and TGF-b) and cytokines (interleukins)

Scar Remodeling

The transition from granulation tissue to scar involves shifts in the composition of the ECM; even after its synthesis and deposition, scar ECM continues to be modified and remodeled. The *degradation* of collagens and other ECM components is accomplished by a family of metalloproteases(so called because they arc dependent

Metalloproteinases include *interstitial collagenases,* which cleave the fibrillar collagen types I, II, and III;*Gelatinases* (or *type IV collagenase},* which degrade amorphous collagen and fibronectin; and *stromelysins,* which catabolize a variety of ECM constituents, including proteoglycans, laminin, fibronectin, and amorphous collagen.

These enzymes are produced by a variety of cell types (fibroblasts, macrophages, neutrophils, synovial cells, and some epithelial cells), and their synthesis and secretion are regulated by growth factors, cytokines, phagocytosis, and even physical stress. Their synthesis is inhibited by TGF-jS and may be suppressed pharmacologically with steroids. Given the potential to wreak havoc in tissues, *the activity of the metalloproteinases is tightly controlled.* Thus, they are typically elaborated as inactive *(zymogen)* precursors that must be first activated; this is accomplished by certain chemicals (e.g., HOC1') or proteases (e.g., plasmin) likely to be present only at sites of injury. In addition, activated collagenases can be rapidly inhibited by specific *tissue inhibitors of metalloproteinase (TIMPs),* produced by most mesenchymal cells.

REFERENCES

[1]. wound healing: a review of the literature. Dermatol Surg 34:1159-1169. Scappaticci FA, Fehrenbacher L, Cartwright T, Hainsworth JD, Heim W, Berlin J, et al. (2005). Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J Surg Oncol 91:173-180.
[2]. Tandara AA, Mustoe TA (2004). Oxygen in wound healing—more than a nutrient. World J Surg 28:294-300.
[3]. Park JE, Barbul A (2004). Understanding the role of immune regulation in wound healing. Am J Surg 187:11-16
[4]. Quattrini C, Jeziorska M, Boulton AJ, Malik RA (2008). Reduced vascular endothelial growth factor expression and intra-epidermal nerve fiber loss in human diabetic neuropathy. Diabetes Care 31:140-145.