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Connective Tissue Alterations: Healing Processes in Periodontitis

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After traumatic or surgical injury, healing is initiated as part of the immediate and acute inflammatory responses. A clot that normally provides hemostasis almost immediately after injury also forms a matrix rich in platelet-derived cytokines that stimulates and facilitates healing In contrast, periodontal infections do not normally produce the massive, platelet-rich clot observed in traumatic injury. Thus the periodontal "healing" cycle during the pathogenesis of periodontal disease is primarily post inflammatory; and cellular elements other than platelets provide important signals in this process. Periodontal repair occurs in overlapping phases of inflammation shut-down, angiogenesis and fibrogenesis. In the postinflammatory healing process, the shutdown of inflammatory processes and initiation of post-inflammatory healing is orchestrated by leukocytes. Some of the important anti-inflammatory signals generated by leukocytes include **IL-1 receptor antagonist (IL-lra)** and **transforming growth factor** - /3

Angiogenesis and fibrogenesis, as well as cytokines such as IL-1/3 and TNF-/3 that help to induce these processes, participate in both inflammation and healing. IL-1/3 and IL-la are indirectly involved in inducing fibroblast proliferation and collagen synthesis by stimulating the production of PGE_2 or the release of "secondary" cytokines such as **platelet-derived growth factor (PDGF)** and TGF-0. PDGF is a protein complex formed by different combinations of *a* and *b* chains, resulting in three isoforms, PDGF-AA, PDGF-AB and PDGF-BB. It is produced by numerous cells and tissues, including endothelium, vascular smooth muscle, and macrophages. PDGF activates fibroblasts and osteoblasts, resulting in the induction of protein synthesis. The PDGFs are related structurally and functionally to **vascular endothelial growth factor** (VEGF), an important factor in endothelial proliferation. VEGF is a glycoprotein produced by many cells, including monocytes/macrophages, and it is induced by anti-inflammatory factors such as TGF-/3.

TGF-/3 is a multifunctional peptide that stimulates osteoblasts and fibroblasts and inhibits osteoclasts, epithelial cells, and most immune cells. Receptors for TGF-/3 are found in almost all cells. TGF-/3 is produced as a propeptide, and activation requires acidic conditions. TGF-/3 is known for its ability to promote the elaboration of fibroblast extracellular matrix adhesion.

Other fibrogenic cytokines that may play a role include basic fibroblast growth factor (bFGF), TGF-a, and TNF-a. TGF-a and TNF-a are produced mainly by cells of the monocyte lineage, and within the periodontium, bFGF is produced primarily by PDL cells and endothelium.

In the healing of alveolar bone, regeneration of bone within a defect clearly can occur. The immune system can induce regenerative bone healing by preventing osteoclast formation and activation and by activating osteoblasts. By blocking osteoclast formation or increasing osteoclast death, it is possible to cause a marked decrease in osteoclastic activity. TGF-/3 is a potent inhibitor of osteoclast formation. Bone matrix itself contains TGF-/3, which is released by osteoclastic resorption, and osteoclasts may provide the acidic conditions necessary for TGF-/3 activation. Osteoclast differentiation and activation are inhibited by interferon-y (IFN-y), which is secreted by NK-cells, T-cells, and macrophages. The main effect of IFN-y appears to be inhibition of IL-1 and TNF-a-induced osteoclast activation. IL-lra also is effective in blocking IL-1 and TNF-a-induced osteoclast activation.

Much research in bone healing has focused on activation of osteoblasts and PDL cells as a means of promoting regenerative healing. Two substances, insulin like growth factor I (IGF-I) and PDGF, have been shown to induce or augment regenerative repair. The insulin like growth factors induces osteoblast growth, differentiation, and synthesis of collagen. Several studies in nonhuman primates indicate that the combination of IGF-1 and PDGF effectively and significantly enhances regeneration of periodontal structures, including new bone and cementum.

HEALING AFTER PERIODONTAL THERAPY

Regeneration, repair, and new attachment are aspects of periodontal healing that ha special bearing on the results obtainable by treatment

Regeneration

Regeneration is the **growth and differentiation of new cells and intercellular substances to form new tissues or parts.** Regeneration takes place by growth from the same type of tissue that has been destroyed or from its precursor. Gingival epithelium is replaced by epithelium, and the underlying connective tissue and periodontal ligament are derived from connective tissue. Bone and cementum are not replaced by existing bone or cementum but by connective tissue, which is the precursor of both. Undifferentiated connective tissue cells develop into osteoblasts and cementoblasts, which form bone and cementum.

Regeneration of the periodontium is a continuous physiologic process. Under normal conditions new cells and tissues are constantly being formed to replace those that mature and die. This is termed *wear and tear* repair. It is manifested by mitotic activity in the epithelium of the gingiva and the connective tissue of the periodontal ligament, by the formation of new bone, and by the continuous deposition of cementum.

Regeneration is also going on during destructive periodontal disease. Most gingival and periodontal diseases are chronic inflammatory processes and, as such, are healing lesions. Regeneration is part of the healing. However, bacteria and bacterial products that perpetuate the disease process and the inflammatory exudate they elicit are injurious to the regenerating cells and tissues and prevent the healing from proceeding to completion.

By removing bacterial plaque and creating the conditions to prevent its new formation, periodontal treatment removes the obstacles to regeneration and enables the patient to benefit from the inherent regenerative capacity of the tissues. There is a brief spurt in regenerative activity immediately following periodontal treatment, but there are no local treatment procedures that promote or accelerate regeneration.

Repair

Repair simply restores the continuity of the diseased marginal gingiva and reestablishes a normal gingival sulcus at the same level on the root as the base of the preexistent periodontal pocket. This process, called *healing by scar arrests* bone destruction without necessarily increasing bone height. Restoration of the destroyed periodontium involves mobilization of epithelial and connective tissue cells into the damaged area and increased local mitotic divisions to provide sufficient number of cells.

New Attachment

Newattachment *is* the embedding of new periodontal lament fibers into new cementum and the attachment of the gingival epithelium to a tooth surface previously denuded by disease. The critical phrase in this definition is "tooth surface previously denuded by disease" . Attachment of the gingiva or the periodontal ligament to areas of the tooth from which they may be removed in the course of treatment or during the preparation of teeth for restorations represents *simple healing* or *reattachment* of the periodontium, not new attachment. The term *reattachment* has been used in the past to refer to the restoration of the marginal periodontium, but because it is not the existing fibers that reattach but new fibers that are formed and attach to new cementum, the term has been replaced by the term *new attachment* Reattachment is currently used only to refer air in areas of the root not previously exposed to the pocket, such as after surgical detachment of the tissues or following traumatic tears in the cementum, tooth fractures, or the treatment of periapical lesions.

Epithelial adaptation differs from new attachment in that it is the close apposition of the gingival epithelium to the tooth surface without complete obliteration of the pocket. The pocket space does not permit passage of a probe. Studies have shown that these deep sulci lined by long, thin epithelium may be as resistant to disease as true connective tissue attachment.

New attachment and osseous regeneration have been a constant but elusive goal of periodontal therapy since beginning of this century. Since the 1970s, renewed laboratory and clinical research efforts have resulted in new concepts and techniques that have moved us much closer to attaining this ideal result of therapy.

Melcher pointed out that the regeneration of periodontal ligament is the key as it "provides continuity between the alveolar bone and the cementum and also because it contains cells that can synthesize and remodel the three connective tissues of the alveolar part of the periodontium."

During the healing stages of a periodontal pocket, the area is invaded by cells from four different sources: oral epithelium, gingival connective tissue, bone, and periodontal ligament.

The final outcome of periodontal pocket healing depends on the sequence of events during the healing stages." If the epithelium proliferates along the tooth surface before the other tissues reach the area, the result will be a long junctional epithelium. If the cells from the gingival connective tissue are the first to populate the area, the result will be fibers parallel to the tooth surface and remodeling of the alveolar bone with no attachment to the cementum. If

bone cells arrive first, root resorption and ankylosis may occur. Finally, only when cells from the periodontal ligament proliferate coronally is there new formation of cementum and periodontal ligament.Several methods have been recommended to improve the likelihood of attaining new attachment.

HEALING AFTER FLAP SURGERY

Immediately after suturing (0 to *24 hours),* a connection between the flap and the tooth or bone surface is established by a blood clot, which consists of a fibrin reticulum with many polymorphonuclear leukocytes, erythrocytes, debris of injured cells, and capillaries at the edge of the wound. bacteria and an exudate or transudate also result from tissue injury.

One to 3 days after flap surgery, the space between the flap and the tooth or bone is thinner, and epithelial cells migrate over the border of the flap, usually contacting the tooth at this time. When the flap is closely adapted to the alveolar process, there is only a minimal inflammatory response.

One week after surgery, an epithelial attachment to the root has been established by means of hemidesmosomes and a basal lamina. The blood clot is replaced by granulation tissue derived from the gingival connective tissue, the bone marrow, and the periodontal ligament.

Two weeks after surgery, collagen fibers begin to appear parallel to the tooth surface. Union of the flap to the tooth is still weak, owing to the presence of immature collagen fibers, although the clinical aspect may be almost normal.

One month after surgery, a fully epithelialized gingival crevice with a well-defined epithelial attachment is present. There is a beginning functional arrangement of the supracrestal fibers.

Full-thickness flaps, which denude the bone, result in a superficial bone necrosis at 1 to 3 days; osteoclastic resorption follows and reaches a peak at 4 to 6 days, declining thereafter. This results in a loss of bone of about 1 mm; the bone loss is greater if the bone is thin.

Osteoplasty (thinning of the buccal bone) using diamond burs, included as part of the surgical technique, results in areas of bone necrosis with reduction in bone height, which is later remodeled by new bone formation. Therefore the final shape of the crest is determined more by osseous remodeling than by surgical reshaping. This may not be the case when osseous remodeling does not include excessive thinning of the radicular bone. Bone repair reaches its peak at 3 to 4 weeks.

Loss of bone occurs in the initial healing stages both in radicular bone and in interdental bone areas. However, in interdental areas, which have cancellous bone, the subsequent repair stage results in total restitution without any loss of bone; whereas in radicular bone, particularly if thin and unsupported by cancellous bone, bone repair results in loss of marginal bone.

Healing after Surgical Gingivectomy

The initial response is the formation of a protective surface clot; the underlying tissue becomes acutely inflamed, with some necrosis. The clot is then replaced by granulation tissue. By 24 hours, there is an increase in new connective tissue cells, mainly angioblasts, just beneath the surface layer of inflammation and necrosis; by with the cells becoming fixed to the substrate by hemidesmosomes and a new basement lamina.

Surface epithelization is generally complete after 5 to 14 days. During the first 4 weeks after gingivectomy, keratinization is less than it was prior to surgery. Complete epithelial repair takes about 1 month. Vasodilation and vascularity begin to decrease after the fourth day of healing and appear to be almost normal by the 16^{th} day. Complete repair of the connective tissue takes about 7 weeks.

The flow of gingival fluid in humans is initially increased after gingivectomy and diminishes as healing progresses. Maximal flow is reached after 1 week, coinciding with the time of maximal inflammation.

Although the tissue changes that occur in postgingivectomy healing are the same in all individuals, the time required for complete healing varies considerably, depending on the area of the cut surface and interference from local irritation and infection. Complete epithelial repair takes about 1 month. Vasodilation and vascularity begin to decrease after the fourth day of healing and appear to be almost normal by the 16^{th} day. Complete repair of the connective tissue takes about 7 weeks.The flow of gingival fluid in humans is initially increased after gingivectomy and diminishes as healing progresses. Maximal flow is reached after 1 week, coinciding with the time of maximal inflammation.

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Healing after Electrosurgery

Some investigators report no significant differences in gingival healing after resection by electrosurgery and re-section with periodontal knives, other researchers find delayed healing, greater reduction in gingival height, and more bone injury after electrosurgery. There appears to be little difference in the results obtained after shallow gingival resection with electrosurgery and that with periodontal knives.

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