Periodontal Wound Healing - Review

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ABSTRACT

Periodontitis is a chronic inflammatory disease primarily caused by bacterial plaque, resulting in destruction of supporting structures of teeth. Various periodontal therapies have been performed to regenerate the lost periodontal tissues. The periodontium is a complex structure composed of specialized tissues that support the teeth, and most periodontal surgeries are invasive procedures, including either regeneration or resective osseous procedures. The aim of this review article is to provide an overview of periodontal wound healing.

INTRODUCTION:

Periodontal disease is a multifactorial inflammatory disease resulting from a dysbiotic microbial community of pathobionts and keystone pathogens which induce the destruction of tissue surrounding the teeth. The primary etiology of this disease remains the imbalance of the oral ecosystem resulting in the predominance of a pathogenic flora belonging to the "red or orange complex" described by Socransky SS et al.[1] In a mature subgingival biofilm, pathobionts produced an array of virulence factors, antigens or derived products capable of escaping host defense mechanisms and inducing cell and tissue damage through dysregulation of inflammatory response.

Periodontal disease is caused by bacteria commonly arranged in biofilm. In general, the oral cavity can host over 6 billion bacteria from over 700 species (500 of which are able to arrange in biofilms), to 200 species present in individual mouth at a given point in time. Oral bacteria composed of both gram-positive and gram-negative bacteria; as well as fungi, viruses, mycoplasma and protozoa.[2]

Dental plaque can be defined as the diverse community of microorganisms found on the tooth surface as a biofilm, embedded in an extracellular matrix of polymers of host and microbial origin .There is a high level of interest in the properties of biofilms and microbial communities across all sectors of industrial, environmental and medical microbiology.[3] Oral biofilm in association with anaerobic bacteria is the main etiological factor in periodontal disease.[4] The oral biofilm consists mainly of microbes and host proteins that adhere to teeth within minutes of a dental oral hygiene procedure. The proportions of strict anaerobic, Gram negative and motile

organisms increase significantly in accordance with increasing severity of disease. Disease activity in periodontal disease may range from slow, chronic, progressive destruction to brief and acute episodic bursts with varying intensity and duration.

PATHOPHYSIOLOGY OF PERIODONTITIS

Periodontitis is host-mediated and microbial associated inflammation that leads to loss of periodontal attachment. The disease's pathophysiology has been characterized in terms of its major molecular pathways, which ultimately result in the activation of host-derived proteinases. It also leads to loss of marginal periodontal ligament fibers, apical migration of the junctional epithelium, and apical spread of the bacterial biofilm along the root surface.[5] It also occurs as inflammation, the spread of inflammation from epithelium to connective tissue takes place laterally and apically resulting in the destruction of collagen fibers. When collagen fibers are destroyed, gingivitis progresses to periodontitis, which is clinically characterized as "attachment loss". Gradually due to the activation of osteoclast cells, bone resorption is initiated leading to gradual tooth loss.[6,7] The development of a polymicrobial biofilm that forms as plaque on the tooth surface is the underlying cause of the disease.[8,9] In order to produce nutrition for their growth and function, periodontal pathogens produce degrading byproducts and enzymes that disintegrate host cell membranes and extracellular matrix.[10,11] Our team has extensive knowledge and research experience that has translated into high quality publications. [12–21] The main aim of this review is to highlight the periodontal wound healing.

HEALING:

Healing is that phase of the inflammatory response that results in the restoration of the disrupted body elements into a new physiologic and anatomic relationship.

Periodontal tissues can be restored by three processes:

- Regeneration
- Repair
- New attachment

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. It is often used in the periodontal literature to describe instances where the structural and functional relationship of damaged periodontal tissues appears to be renewed. [22]

Repair simply restores the continuity of the diseased marginal gingiva and re-establishes a normal gingival sulcus at the same level on the root as the base of the pre-existing periodontal pocket. This process called healing by scar, arrests bone destruction without necessarily increasing bone height. [23]

New attachment is the embedding of new periodontal ligament fibers into new cementum and attachment of the gingival epithelium to a 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 restoration represent simple healing or reattachment of the periodontium, not new attachment. Epithelial adaptation consists of a close apposition of the gingival epithelium to the tooth surface without complete obliteration of the pocket. These deep sulci are lined by long, thin junctional epithelium and may be as resistant to disease as true connective tissue attachment. Unlike other wounded connective tissue which responds to injury by scar formation and poorly oriented connective tissue fibers, the lamina propria regenerates rapidly, and the gingival fiber system is restored. [24]

Wound healing is a complex but systematic process. It is orchestrated by highly ordered cellular cascades that are regulated by a variety of chemoattractants, growth factors, and other chemical regulators, as well as by changing environmental conditions in the wound site. [25]

Wound healing involves:

- Induction of an acute inflammatory response by the initial injury.
- Parenchymal cell regeneration.
- Migration and proliferation of both parenchymal and connective tissue cells.

- Synthesis of extracellular matrix (ECM) proteins.
- Remodeling of parenchymal elements to restore tissue function.
- Remodeling of connective tissue to achieve wound strength.

Healing is by Primary first intention or by second intention.

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 primary union or healing by first intention. [26]

Healing by second intention:

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

Secondary healing differs from primary healing:

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 inflammatory mediated injury. Much larger amounts of granulation tissue are formed. This provides the underlying framework for the re-growth of tissue epithelium. A greater volume of granulation tissue generally results in a greater mass of scar tissue. [26]

Secondary healing exhibits the phenomenon of wound 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.

Third intention (Delayed primary closure):

In healing by third intention, the wound is temporarily left open, usually because of contamination. The wound is then closed after 4 to 7 days, with wound approximation being accomplished by either grafting or flap rotation. In all of these healing categories the timing of wound healing, closure, and techniques vary, but the processes involved and the factors affecting healing are basically the same. [26]

PHASES OF SOFT TISSUE HEALING

1. Inflammatory phase
2. Granulation tissue formation
3. Remodeling

Inflammatory phase:

After tissue injury and blood vessel disruption, hageman factor (XII) gets activated and initiation of the clotting cascade and platelet aggregation takes place. This generates bradykinin and complement-derived anaphylatoxin, such as C5a and C3a. This results in permeability of undamaged vessels adjacent to the injured area, resulting in leakage of plasma proteins and interstitial clot formation in the surrounding tissues. Histamine, Serotonin and Heparin also increase the vascular permeability. All these substances are secreted by the mast cells and heparin is also found in platelets.

Prostaglandin, another inflammatory mediator produced from arachidonic acid are also present at the inflammatory site (PGE1 and PGE2). They increase the permeability of the surrounding blood vessel. They are also known to be chemotactic to neutrophils. The increase in vascular permeability together with the action of inflammatory mediators, such as IL-1 and TNF, activates endothelial cells and increases the adherence properties of endothelial cells for circulating neutrophils, which eventually marginate, cross the vessel wall via diapedesis, and enter the site of injury. [27]

Neutrophils are the first cells to appear within 6-12 hours. They prevent infection by phagocytizing micro-organisms and lysing dead tissues by the release of proteases and lysosomal enzymes. They live only several hours after digesting bacteria and necrotic tissue. In the presence of infection and sepsis, neutrophils are necessary for the healing process, but in an aseptic wound, healing proceeds normally in the complete absence of neutrophils. [28]

Next, macrophages generated within the tissues are converted from circulating monocytes enter the injured area in large numbers. They have long life. They phagocytize and digest pathogenic organisms and function as scavengers for tissue debris, including neutrophils, de-vitalize collagen and fibrin clot. They also release chemotactic agents and growth factors for fibroblasts and endothelial cells, e.g. IL-1 and Macrophage-derived growth factor. They digest material and excrete the products into the surrounding environment. This recycling of ingested material is an efficient method of supplying useful substrate material such as amino acids and simple sugars, which are required for subsequent repair. In fact, collagen deposition appears to be enhanced by the presence of activated macrophages. [29]

Lymphocytes appear in the wound 6 to 7 days after injury but are not as critical as macrophages in the wound healing process. They secrete lymphokines, such as migration inhibition factor, IL-2 and Macrophage activation factor, as such may influence healing directly or increase the function of macrophages. They also secrete chemotactic factors and may stimulate fibroblasts proliferation and collagen deposition. [30]

Granulation tissue formation:

This occurs immediately after the inflammatory phase (i.e. 3 - 4 days after injury). Granulation tissue consists of macrophage, fibroblasts and neovasculature within an oedematous matrix of residual fibrin, fibronectin, glycoproteins, collagen and glycosaminoglycans (GAG's).

Fibroblasts are critical cells in the formation of granulation tissue. They produce collagen and elastin, fibronectin, and GAG's and proteases such as collagenases which have a major role in

tissue debridement and remodeling. Endothelial cell proliferation is important in delivering nutrients and oxygen as well as carrying away toxic waste and metabolic by-products. As healing slows and wound remodeling occurs, capillaries slowly regress, and the highly vascular cell-rich granulation tissue transforms into a white, relatively avascular cell-poor scar.

Hyaluronic acid is a prominent component of the wound matrix. It aids in maintaining wound hydration and also has a role in cellular migration, proliferation and differentiation. Hyaluronic acid is replaced by sulphated GAG's such as chondroitin-4, 6-sulphates, dermatan sulphate and heparin sulphate. These sulphated GAG's contribute to tissue resilience and may have a role in collagen synthesis. Early granulation tissue is composed largely of type III collagen.

Fibronectin is one of the main matrix constituents during early wound repair, it is a glycoprotein produced mainly by fibroblasts and endothelial cells and is also found in serum. It comprises the primary; or provisional, matrix for tissue repair and is an integral part of all connective tissue. Collagen, especially type III is subsequently deposited in the fibronectin-bearing matrix as mature collagen bundles form (such as type I) and fibronectin slowly disappears. It also has a role in blood coagulation by binding to fibrin in the presence of factor XII to form cross-links, which strengthen the fibrin clot.

Matrix formation:

It begins with the process of fibroplasia. Growth factors from platelets and macrophages stimulate the fibroblasts to proliferate and synthesize collagen. Fibronectin also plays an important role in fibroblast migration (Fibroblast appears at the site within 2 days). There is a slow elimination of fibronectin, followed by slow accumulation of large fibrous bundles of type I collagen. Collagen fibrils are composed of molecules arranged in an overlapping configuration. Its strength is augmented through formation of intermolecular cross-links. Collagen macromolecules provide the healing tissue with stiffness and tensile strength.

Remodeling:

This is the final phase of wound healing. Granulation tissue formation continues progressively for months after re-epithelialization has occurred. In addition to providing structural support and

strength to the new tissue, collagen can also alter cell function by acting as a chemoattractant for fibroblasts in vivo and vitro.

In the early stages of scar formation, collagen production exceeds collagen breakdown, leading to a temporarily hypertrophic scar. As the healing process continues and the overlying epithelium thickens and matures, collagenase production increases and collagen breakdown may exceed collagen formation, causing the scar to regress to a thin, dense white tissue. However, if a derangement in the balance between synthesis and degradation occurs, a net accumulation of extracellular matrix results, which may lead to the formation of hypertrophic scars and keloids, conditions more frequently seen in the skin than in the oral cavity. Importantly, the remodeling process is slow and continues for years, resulting in a continued turnover of collagen and remodeling of the scar tissue. [31]

EPITHELIAL HEALING

It occurs in hours after injury. There is migration of undamaged cells from the wound margin. The suspected stimuli for migration are soluble mediators, such as epidermal growth factors, fibronectin. A cell is induced to de-differentiate and migrate when its attachment to neighboring cells is disrupted. Before migration the basal cells lose their intercellular desmosome and develop peripheral cytoplasmic actin filaments. This phenotypic change provides an apparatus for locomotion. Within hours after injury, the surface becomes dry because of the presence of blood clot and evaporation of moisture. Migrating cells do not move through the clot but rather deep to it. These cells secrete proteolytic enzymes that dissolve the base of the clot and permit migration of the epithelium. [32]

If the wound surface is excessively dehydrated, the process of wound healing is slower because of the increased time necessary to complete epithelialization; however, in moist wound environment such as in the oral cavity, the epithelial cells migrate more rapidly than in a wound exposed to air.

Epithelial cells are usually seen within 1 to 2 days after surgery. The connective tissue bed is rapidly covered with regenerated junctional epithelium within 5 to 12 days. The junction to occur is on enamel, cementum or dentin. Listgarten and Ellegaard (1973) showed junctional epithelium attachment on calculus. [33]

CONNECTIVE TISSUE HEALING

Normally, epithelium rests on a matrix consisting of a highly organized basement membrane zone made up of laminin and Type IV collagen. However, after injury, epidermal cells stop manufacturing these components, which are not produced until the cells become stationary and cease to migrate. Meanwhile, the cells migrate over a provisional matrix consisting of fibrin cross linked by fibronectin, elastin, and type I and II collagen which direct the movement of migrating
cells through a process termed contact guidance. Also, keratinocytes deposit their own matrix during the epithelialization process by producing fibronectin, collagenase and other proteases. [34]

BONE HEALING

Composition of bone: Organic components of the bone includes type I collagen embedded in a ground substance of GAGs, largely chondroitin sulphate. It is also linked to some non-collagenous proteins such as osteonectin and osteocalcin. Inorganic components include hydroxyapatite crystals. The principal cells involved in bone formation and remodeling are osteoblasts, osteoclasts and osteocytes. Process of healing is similar to connective tissue healing except that there is calcification of connective tissue matrix in bone healing.

Mucoperiosteal flaps are generally used in association with osseous surgery, not only to gain access to and improve visibility of bone, but also to protect underlying structures during healing in order to minimize the resorptive process and inhibit postoperative sequelae of pain, hemorrhage, infection, and so on. Histologic observation of bone exposed after surgery shows

the immediate formation of a clot over the affected area, particularly over the cut surface of adjacent soft tissues. The blood coagulum consists of the formed elements of the blood and cellular and tissue debris dispersed in a fibrin matrix; it is like a gel-like consistency. The clot on bone is a complex of exudate and cellular and tissue debris, loosely complexed with fibrin. The degraded bone, cellular and fibrillar remnants are later removed by macrophage action when a cover of granulation (reparative) tissue forms over the previously denuded bone surface. The granulation tissue is of periosteal and endosteal origin.

There are three patterns of bone involvement generally occurring in tandem are resorption, resorption and formation, formation (appositional). While the first two steps of this sequence tend to occupy 2^{nd} to 3^{rd} week period. If osseous surgery has been performed, the reaction may be expected to be more intense, since numerous subjacent spaces may have been exposed. The bone resorption is mediated primarily by osteoclasts, which are ordinarily located in resorptive bays in the bone's surfaces. Additional bone loss may be produced via actions of osteocytes and macrophage. Repair of bone becomes most active during the 21^{st} to 28^{th} day period after the surgical procedure. Relatively complete restoration of crestal height is evident in the interdental and furcation areas where numerous marrow spaces remained open after completion of the active resorptive process. [35]

On 2^{nd} day, numerous empty lacunae are seen. Osteocytes and osteoblasts undergo enzymatic degradation and disintegration. The decreased osteoclastic activity can be seen. On 6^{th} to 8^{th} day, osteoclast resorption begins and continues for 10 to 14 days. At 2^{nd} week, bone apposition becomes apparent and continues for 2 to 3 weeks. The new bone gives an appearance of a coarse fibrillar trabeculae termed woven bone. At 3^{rd} week, periodontal ligament width is restored to a width and structural character consistent with its preoperative state. At this week, compact bony plates may be partially restored. Interproximal and furcation areas may have regenerated almost completely, while the radicular surface may have lost much of the original height of bone exposed.

For example, 1 mm of bone resorption buccolingually where the osseous septum is 1 mm thick will eliminate the attachment apparatus at that site. However, the same amount of buccolingual

resorption when the septum is 2. 5 mm thick will result primarily in a reduction of septal thickness but without a loss of periodontal attachment for the tooth.

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