1 Oral Wound Healing: An Overview

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In this Overview, I summarize the main content of each of the chapters in this book. Readers are encouraged to carefully read the chapters for more details and relevant literature.

CLOTTING AND INFLAMMATION (CHAPTERS 2, 3 AND 4)

Wounds are common in oral cavity, caused by either trauma or surgery. Soft tissue wound healing in oral cavity proceeds along the same principles as in other areas of the body such as the skin. Wound healing always starts with the blood clotting that initially seals the wound (Chapter 2). Platelet activation during the primary hemostasis releases a number of important cytokines that start the healing process via chemotactic signals to inflammatory and resident cells. In addition, the fibrin-fibronectin clot provides a provisional matrix that both epithelial cells and fibroblasts can use to migrate to the wound space. If a wound continues to bleed, healing is delayed because of the disturbed formation of granulation tissue. Cytokines released during the clotting phase initiate the inflammatory reaction that provides wound debridement, removing damaged tissue and microbes. During this innate immune response, inflammatory cells that have been recruited to the wound site release more cytokines and chemokines which critically modulate wound-healing outcome (Chapter 3). Macrophages appear to be especially critical cells for wound repair. Interestingly, recent evidence suggests that wound macrophage populations shift over time and cells with different phenotypes orchestrate different phases of wound healing (reviewed in Brancato and Albina 2011). Among the cytokines and other regulatory factors that they release, macrophages secrete vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and transforming growth factor-beta1 (TGF-ß1) which appear to be the most significant regulators of tissue repair.

Persistent inflammation retards wound healing and can lead to the formation of chronic wounds and even to development of cancer (reviewed in Eming et al. 2007). In addition, inflammation seems to dictate the healing quality and outcome of the wound. Adult skin wounds heal with visible scars. Fetal skin wounds, however, heal without scars until late third trimester (Ferguson and O'Kane 2004). The most striking difference between fetal and adult healing is the lack of inflammation in fetal wound healing (Eming et al. 2007). It is

crucial, therefore, to effectively down-regulate the inflammatory process to prevent wound fibrosis and chronic wounds. During the last decade, a number of chemical mediators have been found that regulate the resolution of inflammation (Chapter 4). During the early stage of the inflammatory reaction, pro-inflammatory mediators such as prostaglandins and leukotrienes dominate and they continue to dominate in 'unresolved' chronic inflammatory conditions (reviewed in Serhan 2011). In normal healing of acute inflammation, however, specialized pro-resolving lipid mediators are actively expressed to suppress inflammation (Chapter 4). These mediators include lipoxins, resolvins and protectins which have a variety of functions including suppression of influx of leucocytes, stimulation of uptake of apoptotic cells and activation of antimicrobial mechanisms (Serhan 2011). Resolvins are derived from the long-chain n-3 polyunsaturated fatty acids (PUFA) eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). These compounds are found enriched in fish oils. The levels of resolvins increase in individuals consuming EPA. In addition, low-dose aspirin increases the resolving levels by a complex process involving acetylation of cyclo-oxygenase-2 by endothelial cells that converts EPA to a metabolite taken by the leukocytes which finally further convert it to resolvin (Chapter 4). Interestingly, preliminary studies suggest that oral supplementation of EPA and DHA together with low-dose aspirin may reduced inflammation and improve wound healing in acute human wounds (McDaniel et al. 2011).

Despite the enormous amount of data available about wound healing in general, molecular features of wound healing in different areas of oral cavity are still emerging. A common observation by clinicians is that oral wounds heal quickly and in some areas such as gingiva and palatal mucosa without significant scar formation. These observations are supported by experimental evidence showing that palatal wounds in humans and pigs heal with minimal scarring (Mak et al. 2009; Wong et al. 2009). Although the molecular mechanisms of the scar-free healing in oral cavity are still being dissected, the current evidence points to reduced or fast resolving inflammation that separates scar-free oral wounds from skin wounds that heal with scarring (Larjava et al. 2011a).

RE-EPITHELIALIZATION AND GRANULATION TISSUE FORMATION (CHAPTERS 5 AND 6)

Within 24 hours after wounding, epithelial cells at the margin of the wound dissolve their hemidesmosomal adhesions and show first signs of migration. In 48 hours, proliferation starts behind the leading edge, seeding more cells into the wound site. Epithelial cells migrate through fibrin-fibronectin provisional matrix until they contact the front of leading cells coming from the other side of the wound. This migration is a complex process that depends on cell surface integrin-type matrix receptors. Their expression is induced in the migratory cells to facilitate optimal adhesion strength to the extracellular matrix. This matrix is composed of proteins present in the provisional matrix and those synthesized by the cells, including laminin-332, fibronectin EDA and tenascin C. Too strong adhesion to the matrix would prevent migration and too weak adhesion would not provide sufficient force for migratory movement. When epithelial cells resume this optimal adhesion strength, their migration can be stimulated by a number of cytokines and growth factors such as epidermal growth factor (EGF), heparin-binding EGF (HB-EGF), TGF-ß1 and others. Furthermore, re-epithelialization is also critically dependent on proteolytic enzymes, including plasmin and matrix metalloproteinases. These enzymes support cell migration at multiple levels by breaking down the provisional matrix, loosening up the adhesions and also by activation of

growth factors. The activity of these enzymes needs to be well balanced, as uncontrolled enzymatic activity is associated with chronic wounds that fail to re-epithelialize. Fortunately, most wounds re-epithelialize perfectly with complete regeneration of the epithelial structure and function.

The formation of granulation tissue starts simultaneously with re-epithelialization; however, its maturation to connective tissue takes much longer time and may in fact continue for months if not years. The purpose of granulation tissue is to replace the provisional wound matrix and provide scaffold for connective tissue formation. Small wounds with primary closure heal quickly with fast re-epithelialization and only a small amount of granulation tissue will form. Open wounds, however, heal with slower epithelial closure and more granulation tissue formation. Initially, fibrin-fibronectin provisional matrix contains neutrophil granulocytes that are subsequently replaced by macrophages, lymphocytes and mast cells. Inflammatory cells secrete a number of factors capable of activating and recruiting resident fibroblasts at the wound margin, mesenchymal progenitor cells (pericytes and other mesenchymal stem cells) and circulating fibroblast-like cells (fibrocytes) that migrate to the provisional matrix. These cells, along with cells forming the new blood vessels, form the granulation tissue and subsequently turn it to connective tissue. Analogous to epithelial cell migration, fibroblast migration also depends on induction of certain integrins, new matrix production (e.g. EDA- and EDB-fibronectins, tenascin-C, hyaluronan, type III collagen, matricellular proteins) and expression of several matrix-degrading enzymes. When sufficient amount of collagen is produced into the granulation tissue, wound contraction can start. This process pulls wound margins closer together, reducing surface area and increasing the speed of wound closure. Wound contraction is actively mediated by differentiated myofibroblasts that use integrin receptors to pull the matrix using their strong actin-rich cytoskeleton. Myofibroblasts differentiate from local resident fibroblasts or other progenitor cells in the presence of certain matrix molecules and growth factors including EDA-fibronectin and TGF-ß1. After wound contraction, granulation tissue remodeling takes place. During this process, fibroblasts degrade, remodel and re-organize the extracellular matrix. Altered mechanosensory signals from the remodeling tissue will reduce the cellular activity, and matrix production will cease and myofibroblasts undergo apoptosis. The end result of healing in the skin is often the formation of a connective tissue scar with reduced tensile strength, disoriented collagen fibers and other molecular alterations. In some parts of oral mucosa (gingiva, palatal mucosa), healing results in clinically scar-free healing with histological features of almost normal connective tissue (see above). The molecular differences of these two different healing responses are still not clear.

ANGIOGENESIS (CHAPTER 7)

Angiogenesis (formation of new blood vessels) is tightly associated with granulation tissue formation during wound healing. Injury to the tissue initiates the angiogenic process in the capillary network. Angiogenesis has many similarities to re-epithelialization (see above). Endothelial cells or their precursor cells in the pre-existing venules become activated by humoral factors (see below) and start to migrate to the wound provisional matrix within 24 hours after wounding. For migration, endothelial cells detach from the basement membrane and use their integrin receptors for cell movement. This process is similar to re-epithelialization but involves different integrins. Endothelial cells behind the leading edge start then to proliferate and feed more cells to the developing endothelial bud or sprout.

Finally, proximal to the proliferating and migrating cells, endothelial cells form a tube that is stabilized by surrounding basement membrane. At this stage, the new capillary is ready for blood flow that is necessary for maintenance of the new vessel.

Platelets, inflammatory cells (especially macrophages) and resident fibroblasts release many angiogenic factors, such as vascular endothelial growth factors (VEGFs) that play a crucial role in promotion of angiogenesis. Hypoxia in the wound site is a major inducer of VEGF expression in a variety of cells. The fully formed granulation tissue has a high number of new blood vessels. Some of these vessels need to regress during tissue maturation. This regression is linked to reduced or lack of angiogenic stimulus and also to active inhibition of angiogenesis by various factors, including thrombospondin-1. Balance between angiogenesis and its inhibition may be important for healing outcome. For example, skin wounds that form scars have more robust angiogenesis than palatal mucosal wounds that heal without scars (Mak et al. 2009). On the other hand, poor angiogenic response in wounds of diabetic patients contributes to wound healing morbidity in these patients.

HEALING OF EXTRACTION SOCKETS (CHAPTER 8)

One of the most common oral wounds is an extraction socket after tooth removal. Wound healing in the socket follows similar principles as the soft tissue healing except that it also involves healing of the bone, namely (1) clotting, (2) re-epithelialization, (3) granulation tissue formation and (4) bone formation. Within minutes after tooth extraction a blood clot forms into the extraction socket. Re-epithelialization starts as for any soft tissue wounds as described above. Granulation tissue also forms as explained above and within a week it has replaced the blood clot. What happens next differs from soft tissue healing. Osteogenic cells from the bottom and the walls of the socket are induced to migrate into the developing granulation tissue in which they differentiate and initiate bone deposition. It is likely that mesenchymal stem cells recruited locally together with bone marrow derived cells are induced for osteogenic differentiation by cytokines and growth factors released locally by platelets and inflammatory cells and bone cells. In addition, wounding stimulates osteoclastic activity and remodeling at the socket walls, which process releases growth factors and cytokines such as TGF-ß1 and BMPs that are stored in the bone matrix. Therefore, bony defect turns to bone rather than soft tissue. Most of the socket is filled with bone within 8 weeks after extraction. Bone remodeling continues, however, often for 6 months or more, with great individual variation. During this remodeling phase of socket healing, dimensions of socket walls change. A significant amount of bone height and width is lost due to resorption of the socket walls. The extent of this bone loss is again individual and dependent on several variables such as site, presence of adjacent teeth, treatment protocol and smoking. Grafting the socket with bone substitutes and covering them with membranes appears to show promising results in preventing some of the bone loss after extraction.

FLAP DESIGN FOR PERIODONTAL WOUND HEALING (CHAPTER 9)

Surgical maneuvering of the periodontal soft tissues plays a key role in optimal healing. It is well documented that large scalloped incisions cause significant tissue shrinkage during the healing period. In addition, anterior periodontal surgery with both labial and lingual

opening of the flap frequently results in loss of papillary fill and creates so-called black holes. Furthermore, use of membranes and bone grafting materials makes it difficult to achieve primary closure, leading to membrane exposure and loss of bone grafting material. Different surgical techniques have been developed to optimize primary closure and therefore protect the fibrin-fibronectin clot that plays a crucial role in wound stability and healing outcome. Avoiding surgical incisions that compromise the integrity of the interdental supracrestal soft tissue seems to improve preservation of the interdental papilla. Various papilla preservation techniques have been designed and they seem to limit graft or membrane exposure as well as maintain the papilla. These techniques work well when adequate width of the interdental space is available. Since the interdental space is not often sufficiently wide for papilla preservation technique, a single flap approach could be considered. In this technique, only the buccal or lingual flap is elevated, allowing the flap to be repositioned to its original height with primary closure. Flap elevation from the bone is minimized. Specially designed micro surgical instruments can be used for these procedures. As for any surgical procedure, a key for success is a high level of oral hygiene before and after the surgical procedure to reduce the amount of microbial biofilm at the wound site, leading to reduced inflammatory reaction in the healing wound.

REGENERATION OF PERIODONTAL TISSUES (CHAPTERS 10 AND 11)

Conventional periodontal surgery aimed at reduction of periodontal pockets results in repair of periodontal structures that no longer mimic the normal architecture of the healthy periodontium. Periodontal regeneration is, however, a wound healing process that reproduces all the lost structures of the periodontium, namely alveolar bone, cementum, periodontal ligament and gingiva. Although wound healing at the tooth–gingiva interphase follows the same principles as in the skin or palatal mucosa, there are key differences that influence the healing outcome. In periodontal healing, the fibrin-fibronectin clot needs to be stabilized on a mechanically debrided root surface. This stabilization often fails leading to migration of the epithelium along the root surface, thus preventing connective tissue healing and regeneration. Periodontal ligament and bony walls of the tissue defect appear to serve as niches from which the progenitor cells migrate into the regenerating periodontium. Therefore, the defect configuration plays a critical role in periodontal regeneration. Stabilization of the wound and providing space are key elements for successful regeneration. Space can be provided by various barrier membranes or even bone grafting materials or other devices (see below). As indicated in the previous chapter, primary wound closure and appropriate control of microbial biofilm and thereby inflammation are crucial elements for successful regeneration.

Barrier membranes for space maintenance are cumbersome to use, make it difficult to achieve primary closure and often provide only partial regeneration. Therefore various biological agents have been developed to promote periodontal regeneration. At the present time, three different products are in clinical use and recommended for periodontal regenerative procedures. These are platelet-derived growth factor-BB (GEM 21S[®]; Osteohealth), type I collagen-derived synthetic peptide (PepGen P-15[®]; Dentsply) and enamel matrix protein mixture (Emdogain[®], Straumann). Although the mechanisms explaining how these agents function when applied to the periodontal lesion are still unclear, they seem to produce positive clinical results. They do seem to share some common properties such as promotion of proliferation of fibroblasts and osteogenic cells. In addition,

they all seem to positively promote stem cell recruitment. Other agents are also being tested for clincial use in humans, such as fibroblast growth factor-2 (FGF-2) and growth and differentiation factor-5 (GDF-5), with promising results. A common feature for all these agents is a large heterogeneity in treatment outcomes that could result from suboptimal release of the active ingredient (dose and time) from the scaffold. In addition, patient, site, type of defect and clinical application may critically influence the outcome. Since stem cell recruitment seems to be critical for the regenerative therapy, mesenchymal stem cells have been directly added into the periodontal defects in experimental setting. These studies have shown that this therapy may produce some regeneration of the periodontium. Future studies are needed to optimize these techniques and also to better explain the biological mechanisms that determine treatment outcomes and regeneration process.

OSTEOINTEGRATION AND SOFT TISSUE HEALING AROUND DENTAL IMPLANTS (CHAPTER 12)

Dental implants have become part of routine treatment in oral rehabilitation. Placing an implant into the alveolar bone initiates a wound healing response that typically involves healing of both soft tissues and bone. Implant fixtures can be placed at the level of the alveolar bone crest or left above it. They can also be either covered completely with the mucosal tissue or left exposed to oral cavity with a healing abutment. Wound healing response varies depending on the situation. In cases where an implant is placed at the level of bone with a cover screw and then completely covered with soft tissue with primary closure, the soft tissue will quickly heal following the principles described above with minimal granulation tissue formation. Wound healing reaction in the osteotomy site is initiated by clot formation at the inner parts of the treads. This clot is then infiltrated by inflammatory cells, namely polymorphonuclear leukocytes and macrophages. Fibroblastic progenitor cells then invade the provisional matrix and deposit granulation tissue that gets vascularized by migrating endothelial cells. These cells then differentiate to osteoblasts and start to deposit bone. Bone deposition can be seen as early as 4 days after implant placement, but complete osteointegration with maximum bone–implant contact takes 1–3 months. Implant stability can be tested during healing with various devices. Bone around the implant continues to remodel over the first year of implant placement and is dependent on the mechanical stress from occlusal forces. Osteointegration of dental implants is a very predictable procedure with success rates far above 90%, regardless of the implant loading protocol. Failure to osteointegrate or the development of peri-implant disease are often connected with patient-associated factors such as smoking, diabetes and history of periodontal disease, which can all affect various phases of the initial wound healing response (Mellado-Valero et al. 2007; Heitz-Mayfield and Huynh-Ba 2009).

When implants are immediately 'restored' with a healing abutment or a permanent abutment and restoration, the soft tissue healing response will differ from that associated with covered implants. In this case, a blood clot forms now between the abutment or the collar of the implant and the gingival soft tissue. During healing, epithelial cells from oral epithelium migrate towards the implant/abutment, flatten along the surface and create a peri-implant epithelium that mimics junctional epithelium. The adhesion of this epithelium may not fully recapitulate that of junctional epithelium (reviewed in Larjava et al. 2011b). During healing, fibroblasts apical to the peri-implant epithelium deposit collagen fibers that run parallel to the implant surface without insertion into the implant surface. This can be explained by the

lack of cementum formation at the connective tissue–implant interphase. Several studies have shown that when the implant/abutment interphase is moved away from the bone crest, less crestal bone resorption will occur. It is probable, therefore, that soft tissue attachment to the abutment (or the implant) is not sufficiently strong to prevent biofilm penetration to the micro gap between the abutment and the implant. Future studies are needed to develop implant surface characteristics for better attachment of the soft tissue during the healing process. Improved therapy protocols are also needed to avoid multiple intrusive manipulations at the abutment/implant–soft tissue interphase that predispose the healing tissue to physical and microbiological insults.

THE PULP HEALING PROCESS (CHAPTER 13)

Wounding of the dental pulp happens commonly in a dental practice. Preparation of teeth for removal of caries and subsequent restoration or for bridge abutments often leads to traumatic injury or exposure of the pulp. If the injury is sufficiently weak and does not destroy the odontoblast layer, the cells are activated to produce tertiary dentin to protect the healing pulp from further injury. Bacterial products, cytokines released from the resident and inflammatory cells as well as growth factors of the TGF-ß family released from the dentin matrix are all able to stimulate this reactionary dentinogenesis. When the pulp is exposed with the damage to the odontoblast layer, healing process with a dentin bridge is possible but requires recruitment of progenitor cells that can differentiate to odontoblasts. Although reparative dentinogenesis can happen spontaneously in the absence of bacteria, many materials have been used to stimulate the reparative dentin formation. Traditionally, calcium hydroxide has been used for pulp capping after exposure. More recently, mineral trioxide aggregate (MTA) has been recommended for this purpose. Steps of wound healing in the pulp after calcium hydroxide application have been well characterized. Application of calcium hydroxide leads to superficial necrosis of the pulp followed by inflammatory reaction. Within a week the inflammatory layer is replaced by granulation tissue with numerous fibroblasts and blood vessels. Stem or progenitor cells are then induced to proliferate and migrate to the wound site where they differentiate into odontoblast-like cells that are able to synthesize proteins and vesicles involved in formation of reparative dentin. The origins of the stem/progenitor cells are still under investigation. If the inflammation persists in the pulp, the development of reparative dentin is inhibited and pulpal necrosis may follow. Future studies are likely to lead to new therapeutic approaches for pulp capping that further promote reparative dentin formation.

DERMAL WOUND HEALING AND BURN WOUNDS (CHAPTER 14)

As described in previous chapters, healing of relatively small traumatic or surgical soft tissue wounds usually results in fast repair with formation of a small scar, or in some cases in regeneration of the affected tissue. In contrast, thermal injuries in skin or mucosa may often cause more extensive damage, leading to severely compromised wound healing outcomes. The extent of thermal injury depends on temperature, contact time, thickness of the skin or mucosa and vascularity of the area. The central area of a burn wound shows necrosis often called the zone of coagulation. Necrotic area is surrounded by the heat-injured

tissue that is still alive but has reduced tissue perfusion (zone of stasis). This area has potential for recovery if tissue perfusion can be re-established. The zone of hyperemia surrounds the zone of stasis and is characterized by viable cells and vasodilatation caused by inflammatory reaction. Burn injuries continue to progress into deeper structures for 48–72 hours after the initial insult. This is caused by vascular and inflammatory reactions. While the superficial wounds heal by re-epithelialization, the deeper wounds require surgical treatment for healing. To this end, all non-viable burn tissue will be removed and various skin grafts, artificial skins or flaps are used to reconstruct the area. The type of graft or whether flaps are utilized depends on the area and depth of the injury.

Superficial intraoral burn wounds are common and often caused by hot drinks. Fortunately, these wounds heal without complications and require no treatment. Deep intraoral wounds, however, are challenging to treat and numerous surgical procedures may be required to reduce the contractures that often develop to the commissural areas. Deep facial burns are also problematic as they often heal with visible scars that interfere with speech and expression of emotions. Such scars can have a detrimental effect on oral functions and also cause psychological trauma. Future burn therapies should focus on novel techniques for scar reduction, especially in the facial area.

HEALING OF LARGE DENTOFACIAL DEFECTS (CHAPTER 15)

Dentofacial defects are bone and soft tissue deficits in the jaws or other bones of the skull. They can result from congenital defects, trauma or tumors. Reconstruction of these defects can be challenging, as often a significant amount of new bone and soft tissue need to be engineered. Most bone defects require grafting with block or particulate grafts that can be harvested from the patient. Alternatively prepared cadaver bone graft materials or synthetic bone particles could be used. The bone graft is then completely covered with a resorbable or non-resorbable barrier membrane to prevent soft tissue invasion into the graft site. Graft site vascularity and wound stability are key factors for successful outcome. Lateral ridge augmentations and sinus elevation procedures are typical examples of bone grafting procedures aiming at augmentation of the alveolar ridge for implant placement. While sinus floor and lateral ridge augmentations are relatively predictable procedures, vertical augmentation of alveolar defects remains difficult and often unpredictable. Distraction osteogenesis has been used successfully to augment atrophic alveolar bone. This technique is, however, labor intensive and associated with significant morbidity and hardware costs.

Recently, synthetic bioimplants combined with growth factors have been considered for reconstruction of craniofacial defects. These implant materials contain bone morphogenic proteins (BMPs) that are known to support bone formation. Two products are currently in clinical use, namely BMP-7 (BMP-7, Stryker, Allendale, New Jersey, USA) and BMP-2 (BMP-2, Medtronic, Fridley, Minnesota, USA). BMP-2 has been approved by the US Food and Drug Administration (FDA) for anterior lumbar spinal fusion, sinus elevation and lateral ridge augmentation. BMP-7 device has been approved for posterolateral lumbar spine fusion and treatment of long bone non-union fractures. Both products use type I collagen as their carrier. Positive results with BMP-2 in sinus floor and lateral ridge augmentations have been reported (Jung et al. 2009; Triplett et al. 2009). In addition, positive results using BMP-7 in demineralized bone matrix for treatment of mandibular resection defects have been published (Clokie and Sándor 2008). Future studies should

further evaluate the effectiveness of these products in the reconstruction of various defects in the craniofacial area when combined with autogenous mesenchymal stem cells (Sándor and Suuronen 2008).

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