Chapter 12 Inflammation and Bone Healing Around Dental Implants

The integration of dental implant materials with bone takes advantage of the fact that bone is able to heal with new bone following injury. Furthermore it can do so in very close apposition with certain metals and ceramics—for example, titanium or hydroxyapatite—without an intervening layer of less differentiated connective tissue. The implantation of titanium into bone initiates a wound healing process very similar to that which occurs when bone forms via the membranous pathway and later when bone remodels and repairs itself. This chapter reviews the basic processes in bone biology as they relate to bone formation, homeostasis, remodeling, and repair, and finally the events that occur at the bone-implant interface.

BONE FUNCTION AND STRUCTURE

Among the numerous functions now attributed to bone, structural integrity and protection remain central. Mature bone is made up of two distinct calcified compartments, an outer cortical or compact shell and an inner trabecular or cancellous core. Cortical bone is tightly organized in a series of concentric calcified rings or lamellae organized around a central canal containing blood vessels, lymphatics, nerves, and connective tissue. Embedded in islands or lacunae within these lamellae are osteocytes. Whereas cancellous bone is highly mineralized and poorly vascularized, trabelcular bone is much less mineralized but highly vascularized. Trabecular bone is composed of an interconnected latticework of mineralized trabeculae with the trabeculae organized parallel to lines of stress. Again, osteocytes are embedded in lacunae within the trabeculae. The outer layer of cortical bone is sheathed in a specialized connective tissue, periosteum.

Periosteum is composed of an outer fibrous layer and an inner cellular layer. While the outer layer has no osteogenic potential, the inner layer that is in contact with the bone is home to osteoblasts and their precursors as well as osteoclasts and their precursors. Similarly, the inner endosteal surfaces of trabeculae and cortical bone are also surrounded by a connective tissue layer, endosteum, that again contains osteoblasts and osteoclasts and their progenitor cells.

Bone Homeostasis

Appearances aside, bone is a dynamic organ undergoing constant remodeling and adaptation in response to mechanical, systemic, and local factors. This process involves the closely coupled destruction of existing bone by osteoclasts followed by deposition of new bone by osteoblasts. If either of these processes—destruction or formation—is interrupted, pathology is observed. Bone multicellular units (BMU) comprised of osteoblasts, osteoclasts, and osteocytes are responsible for maintaining bone homeostasis and for repair and regeneration following injury.

Osteoblasts and Osteocytes

Osteoblasts are derived from mesenchymal tissue along a tightly regulated pathway. Mesenchymal cells can form connective tissue fibroblasts, adipocytes, and bone. Differentiation of mesenchymal cell into osteoblasts occurs along a pathway involving regulation by autocrine, paracrine, and endocrine factors. Endocrine factors including parathyroid hormone, growth hormone, and insulin-like growth factor stimulate proliferation and in certain instances differentiation for pre-osteoblastic cells.

Critically, RUNX2, a nuclear transcription factor, must be expressed for a mesenchymal cell to differentiate along an osteoblastic lineage. The mechanisms by which expression of RUNX2 lead eventually to an osteoblast phenotype is beyond the scope of this chapter. However, it should be noted that bone morphogenetic proteins (BMPs) are critical for the induction of RUNX2 expression. BMPs are a member of the transforming growth factor family of proteins, and to date 30 have been identified. BMPs are present in bone and become soluble following demineralization. At that point they are able to exert inductive effects on differentiating cells in the osteoblast lineage. Thus, bone formation, at least in adulthood, is critically dependent on bone destruction occurring first. Several existing and emerging therapeutic approaches in bone grafting are intended to introduce autogenous BMPs, allogenic BMPs, or more recently, recombinant BMPs to a surgical site.

Once fully differentiated, osteoblasts synthesize an extracellular matrix principally composed of type 1 collagen but also containing other molecules. This matrix eventually becomes calcified and the osteoblasts are encased within the mineralized tissue. At that point the osteoblast is called an osteocyte. Osteocytes communicate with one another via dendritic processes, and the function of viable osteocytes with bone appears to be one of mechanosensation. Thus, bone that is not being mechanically stimulated tends to atrophy, while the converse is true of bone stimulated by exercise.

Osteoclasts

Osteoclasts are multinucleated cells of hematopoietic lineage, specifically of the monocyte/macrophage lineage. Differentiation of monocytes to osteoclasts requires physical contact with osteoblasts or stromal cells. Osteoblasts express receptor activator of nuclear factor κβ-ligand (RANKL) on their membrane surface, which binds to the RANK receptor on osteoclast precursor macrophages and induces them to differentiate and eventually fuse into multinuclear cells, called osteoclasts. Osteoblasts also produce monocyte colony stimulating factor (M-CSF), which stimulates proliferation of osteoclast precursors. Whereas RANKL binds to RANK and stimulates osteoclastogenesis, the soluble molecule and decoy receptor osteoprotegrin (OPG) competitively binds RANKL and inhibits osteoclastogenesis. The relative proportions of RANKL and OPG have been termed the RANKL/OPG axis and seem to be instrumental in inflammation-dependent bone loss. This is especially significant for maintaining long-term stability of bone levels around the osseointegrated implant. This will be discussed later in this chapter.

BMUs

Osteoblasts, osteoclasts, and osteocytes are organized into BMUs. These units are organized as cutting cones, which are led by osteoclasts that resorb bone and are trailed by osteoblasts that lay down new bone and eventually become osteocytes. BMUs have a limited life span and new units are continually formed to replace old, inactive ones. In good health, about 3% to 5% of an individual's skeleton is being replaced at any given time and there is a relative homeostasis between bone formation and resorption.

BONE HEALING FOLLOWING IMPLANT PLACEMENT

Osteotomy preparation for implant placement, and implant placement itself, results in the destruction of both trabecular and cortical bone. It should be noted that the proportion of each varies such that a much higher percentage of cortical bone is present in the anterior mandible vs. the posterior maxilla. Whenever an implant is placed, there will be regions where the implant is in direct contact with the bone and areas where there are gaps. The areas with gaps are initially filled with blood clot and bone debris, which eventually give way to bone formation. These gaps may be evident only at a microscopic level or, in the case of immediate implant placement, they may be 3 mm or more. It has been shown by Botticelli et al. (2004) and Paolantonia et al. (2001) that gaps of 2 mm and perhaps as large as 5 mm can be expected to heal with osseointegration, even in the absence of membranes or grafting materials.

The areas of bone implant contact provide initial primary stability. However, Roberts et al. (1988) have shown that there is at least 1 mm of necrotic bone adjacent to an osteotomy site, even with optimal surgical technique, and that bone initially in contact with the implant remodels before integrating. In humans, the remodeling cycle, or sigma, is about 4.5 months. In other words, 4.5 months are required for osseous resorption, osteogenesis, and subsequently resorption. Hoshaw et al. (1997) have shown that the rate of bone remodeling increases following implant site preparation. Initial implant loading protocols of four months in the mandible and six months in the maxilla were based on the concept of sigma (Branemark et al., 1977). However, the success of contemporary protocols that emphasize much shorter or even immediate loading suggests that complete remodeling is not a requirement for long-term implant success (Esposito et al., 2007).

Given that de novo bone formation is required along the length of the implant, Osborn and Newesely (1980) have described two ways in which this may occur. Contact osteogenesis describes the formation of bone in direct apposition to the dental implant, whereas distance osteogenesis describes formation of bone from the mineralized surface toward the implant surface (Davies, 2003) (Figure 12.1). Davies has discussed extensively the benefits of contact osteogenesis vs. distance osteogenesis (Davies, 2003). A series of papers from his group, as well as others, have shown that where gaps occur, fibrin adherence to the implant surface is critical for de novo bone formation on the implant surfaces—contact osteogenesis—and that this adherence is improved when the implant surface is textured as opposed to machined. Methods for texturing have included acid etching, sand blasting, electrolysis, plasma spray, and coating with hydroxyapatite. The relative advantages and disadvantages of each surface treatment are beyond the scope of this volume, but in terms of bone implant contact (BIC), all have been shown to be superior to machining (Cochran, 1999).

A matrix is required for bone to form. In non-endochondral bone formation, this matrix is usually preexisting bone. In the case of implant placement, it has been shown that fibrin can be used as a matrix. Osteoblasts migrate through fibrin to the implant surface and first deposit a thin layer of glycoprotein similar to a cement line seen at the junction of old and newly formed bone. Bone is then deposited on the surface of the implant itself; this is contact osteogenesis.

Conversely, no blood clot is present in areas where bone is initially in contact with the implant. Rather, the necrotic bone that results for the osteotomy preparation serves as the substrate for new bone formation. As a result, bone forms from the surface of the bone toward the implant. Distance osteogenesis is expected to predominate in cortical bone, given its more dense nature, vs. trabecular bone.

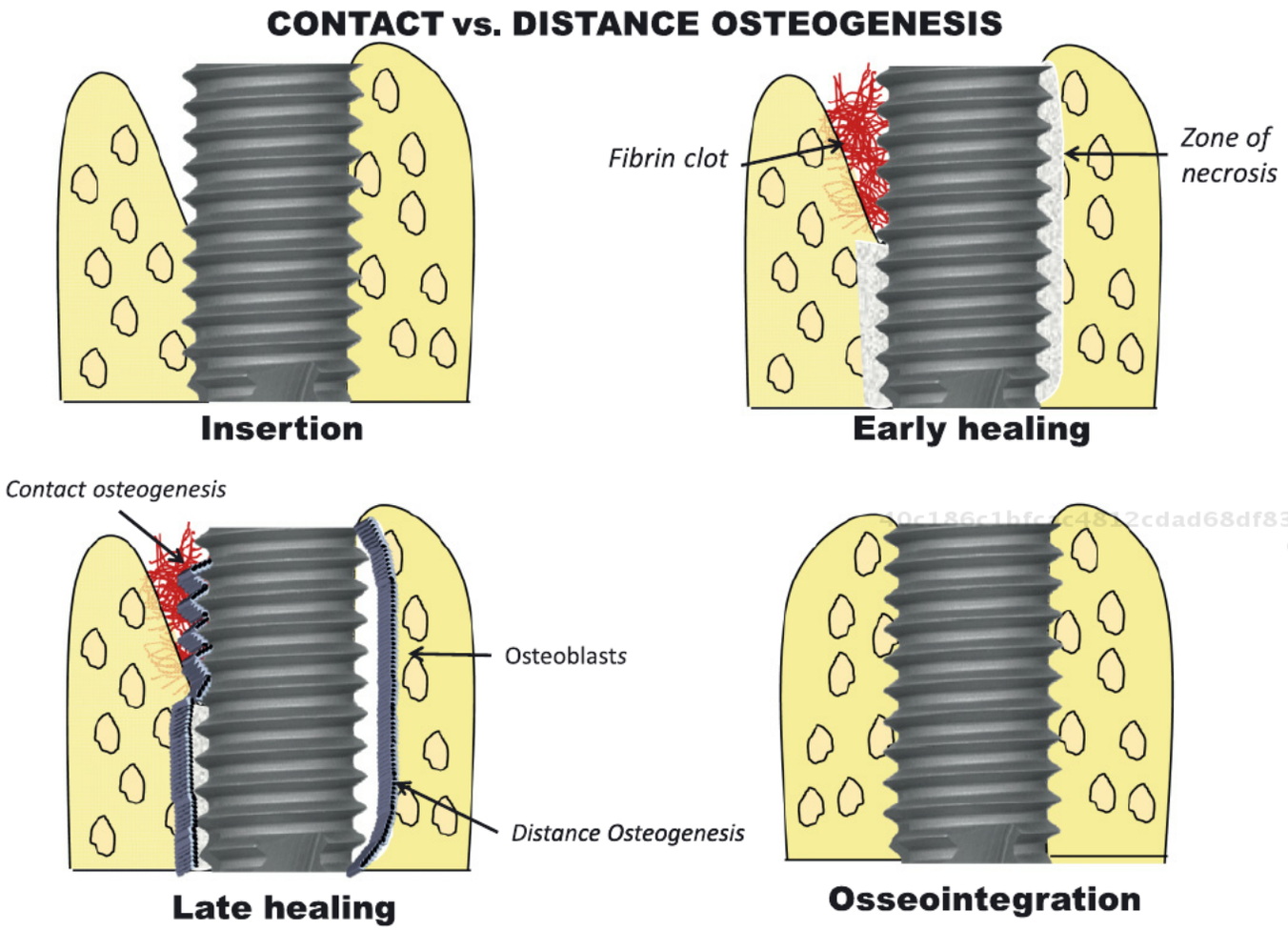

Figure 12.1. Contact vs. distance osteogenesis leading to osseointegration.

INFLAMMATORY BONE LOSS AROUND THE INTEGRATED IMPLANT

Whether by contact or distance osteogenesis, osseointegration is normally expected to result. However, bone is a dynamic structure and maintenance of integration is an ongoing dynamic process. Homeostasis and stability of bone around an implant is characterized by an absence of inflammation.

The precipitating causes of peri-implant bone loss are not entirely clear. Known periodontal pathogens have been localized to peri-implant lesions associated with a progressive crestal bone loss similar to periodontal disease, peri-implantitis. Excessive force or stress has been implicated at least in animal models in the loss of peri-implant bone, but this evidence is equivocal (Isidor, 1996; Kozlovsky et al., 2007; Heitz-Mayfield, 2008). Smoking and diabetes have been suggested as risk factors for peri-implantitis, as they are for periodontitis (Heitz-Mayfield, 2008). A very interesting study recently published by Heckmann et al. (2006) suggests that the presence of both stress and inflammation together induce peri-implant bone loss more than either factor on its own.

While periodontal bone loss and peri-implant bone loss are not the same disease, there are important similarities. These include the presence of periodontal pathogens in both lesions, progressive bone loss over a long period of time and often in the absence of obvious local predisposing factors, and the presence of inflammation (Van Dyke and Sheilesh, 2005; Heitz-Mayfield, 2008).

Periodontal bone resorption has been shown to be caused by inflammation as opposed to bacterial lytic enzymes. The OPG/RANKL/RANK axis has been suggested as a mechanism for understanding the dynamics of bone formation and resorption, particularly as it relates to loss of bone around teeth, and this may have important implications for the management of bone loss around implants (Cochran, 2008). As discussed above, RANKL promotes the resorption of bone, whereas OPG interferes with this process by binding to RANKL and thus preventing the binding of RANKL to RANK

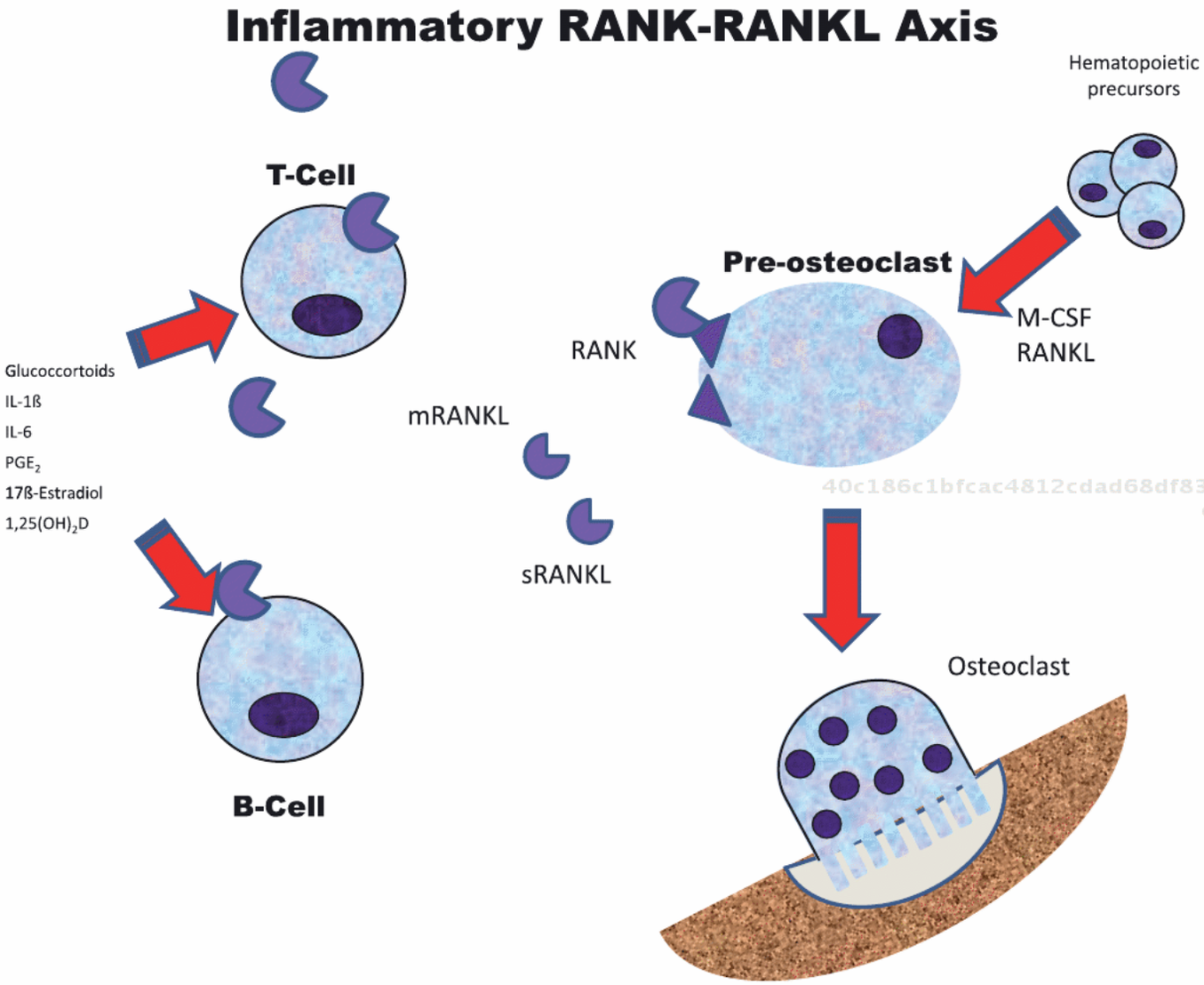

Figure 12.2. The inflammatory RANK-RANKL axis.

(Figure 12.2). In the absence of RANKL-RANK binding, osteoclast differentiation does not occur and osteoclast apoptosis increases. Stability of the ratio of OPG/RANKL is expected in homeostasis, where neither bone formation nor loss occurs. Increased bone formation is expected to be the result of an increase of OPG relative to RANKL, and an increase of RANKL relative to OPG is expected to result in an increase in bone loss. As was discussed earlier, in classical models, RANKL is produced by osteoblasts, then binds to RANK on osteoclasts, induces osteoclast differentiation and bone resorption, and inhibits osteoclast apoptosis. OPG, which is also produced by osteoblast, binds to RANKL, and in so doing prevents it from binding to RANK. This provides the coupling mechanism between bone formation and resorption in homeostatic conditions.

There is an alternative pathway for production of RANKL that does not involve osteoblasts and results in the net loss of bone. It has been shown that T- and B-lymphocytes and fibroblasts also produce RANKL, and that this occurs in response to stimulation by pro-inflammatory molecules including IL-1, IL-6, PGE_2, and TNF-α. Production of RANKL by inflammatory processes such as these results in increased RANKL relative to OPG; osteoclast-mediated bone loss is stimulated in the absence of bone formation and the result is the net loss of bone.

Ongoing loss of peri-implant bone (Figure 12.3) may similarly be characterized not only by a state of inflammation but also by a failure of inflammation to resolve (Van Dyke, 2008). The most up-to-date research has begun to make it clear that the resolution of inflammation is an active process, just as is the development of inflammation, and that specific molecules including IL-4, -10, -12, -13, and -18 as well as Interferon-β (IFNβ) and -γ (IFN-γ) all play an important role in promoting this process. In addition, a new class of polyunsaturated fatty

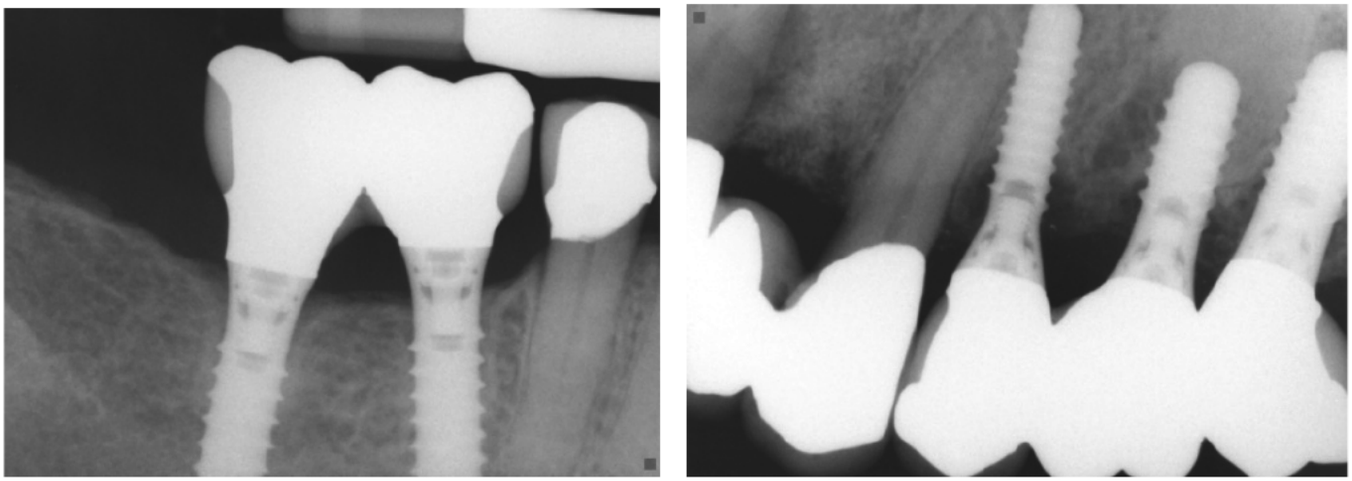

Figure 12.3. Radiographs showing normal bone height (left) and bone loss around implants (right).

acids (PUFA) present in fish oil has been implicated in the resolution of inflammation. These molecules have been termed lipoxins, protectins, and resolvins, and have been shown in in vitro and in in vivo animal studies to promote resolution of inflammation (Serhan et al., 2008).

Early studies showed that using nonsteroidal antiinflammatories (NSAID) to interfere with the production of proinflammatory molecules such as PGE_2 mitigated periodontal bone loss in humans and animals (Jeffcoat et al., 1995). Unfortunately, undesirable side effects preclude the use of these medications over the long term. Lipoxins, protectins, and resolvins and our understanding of them has shed important new light on the dynamics of resolution of inflammation and hold special promise as the basis for a new class of therapeutic agents in the future. These may have a significant impact on the management of inflammatory bone loss in the oral cavity.

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