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The Role of Chemokines and Cytokines in the Pathogenesis of Periodontal and Periapical Lesions: Current Concepts

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1. Introduction

The oral cavity is a complex environment that may harbor more than 750 bacterial species. Proper oral hygiene is essential to maintain the equilibrium of microbial community and oral health. The ecological balance can be compromised in inadequate microbial control situations and an oral infection can be evoked. The bacteria can aid in the formation of dental plaque and caries, leading to periodontal disease (PD) and periapical lesion (PL). PD is the most common chronic inflammatory disorder of microbial origin that affects tooth-supporting tissues including the periodontal ligament and the alveolar bone. Dental caries is characterized by demineralization of enamel and dentine produced by microorganisms' acids. This process can cause pulp necrosis and root canal infection and the progression through the root apex can induce PL. PD and PLs constitute inflammatory and immune response against oral pathogens. Both processes encompass pathogenic mechanisms of inflammation-mediated soft tissue destruction and bone resorption. The etiopathogenesis of these diseases have been extensively investigated over the last decades and the role of several cell types, cytokines and pathways has been described (Graves, 2008, Graves et al., 2011a, Nair, 1997).

Last decades research have documented the importance and commitment of immune system to protect the host from pathogen and also the paradoxical effect accounting for the bone resorption observed in these diseases. More recently, the pattern of immune cell response involved in the lesions progression (i.e. Th1, Th2, Th17, Th9 or T regulatory) has received particular attention (Cardoso et al., 2009, Colic et al., 2009a, Gaffen & Hajishengallis, 2008, Ohlrich et al., 2009, Queiroz-Junior et al, 2011). Although chemokines and cytokines are pivotal to determine these Th patterns, not much is known regarding the expression of these markers in the regulation of bone resorption in sites of PD and PL. This

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chapter will cover the findings regarding the pathways involved in soft and mineralized tissue destruction and present hypotheses that integrate this information into a context of inflammatory/immune host response.

2. Periodontal and periapical lesions etiology: Similarities and peculiarities

The oral cavity is replete with surface-associated communities of microorganisms – the biofilms – colonizing mucous membranes, dental materials and teeth, and these oral biofilms are strongly associated with the etiology of oral inflammatory diseases, such as PD and PL (Beikler & Flemming, 2011). Despite this association, bacteria alone are not sufficient to cause disease. Both lesions of periodontal and endodontic origin involve the host response to bacteria and the formation of osteolytic lesions. Also, additional factors that benefit the microbial community or make the host more susceptible are determinant for PD and PL to develop and progress (Graves, 2008, Nair, 1997).

PDs are the pathological manifestation of the host response against the bacterial challenge from the dental biofilm (Sanz & van Winkelhoff, 2011). PD is a chronic inflammatory condition of the attachment structures of the teeth – alveolar bone, periodontal ligament, connective tissues of gingiva – initiated and perpetuated by predominantly Gram-negative, anaerobe or microaerophilic bacteria that colonize subgingival area – such as *Porphyromonas gingivalis*, *Tannerella forsythia* and *Aggregatibacter actinomycetemcomitans*. These bacteria trigger the destruction of tooth supporting tissues leading to the formation of periodontal pockets, conversion of junctional epithelium to pocket epithelium which culminate with tooth loss (Page et al., 1997). But bacteria mostly cause such tissue destruction indirectly, through the perturbation of the homeostasis between the subgingival microbiota and the host defenses in susceptible individuals. Although bacteria are essential, they are insufficient for the disease to occur (Graves, 2008). For PD, both endogenous risk factors – genetics (Michalowicz et al., 2000), diabetes mellitus (Emrich et al., 1991), rheumatic disorders (Pablo et al., 2009) – and exogenous risk factors – cigarette smoking (Bergström, 2004) and psychological stress (Monteiro da Silva et al., 1996) – may even outweigh the bacteria as determinants of whether the disease occurs and of the severity of clinical outcome.

In the presence of the microbial challenge, the susceptible host responds with an immediate inflammatory and immune response in order to control the challenge. The initial host response comprises an innate recognition of microbial components – lipopolysaccharides (LPS), bacterial DNA – by host cells of the gingiva and the subsequent production of inflammatory mediators, such as eicosanoids (Offenbacher et al., 1986), reactive oxygen species (Chapple, 1997), matrix metalloproteinases (MMPs) (Garlet et al., 2006), chemokines (Silva et al., 2007) and cytokines (Garlet, 2010), which are directly responsible for PD pathogenesis. In addition, periodontal bacteria also lead to the polarization and activation of antigen-specific lymphocytes and migration of other inflammatory cells to periodontal tissues, characterizing an adaptive response (Cutler & Jotwani, 2004). In fact, the development of the PDs seems to be related to the progression of the inflammatory cell infiltrate into the deeper periodontal tissues since the blockade of such inflammation reduces disease process (Graves et al., 1998). These responses, although directed against bacteria, perpetuate and mediate the destruction of connective and mineralized periodontal tissues, being the main responsible for periodontal breakdown (Garlet, 2010).

As for PD, mounting evidence indicate that PLs are also biofilm-induced diseases influenced by the host immune response (Nair, 1997). The distinction for PD is that PLs are initiated as a response to microorganisms present inside the tooth, specifically in the dental pulp

(Ricucci & Siqueira, 2010). Thus, lesions of endodontic origin pose a particular challenge since that bacteria persist in a protected reservoir that is not readily accessible to the immune defenses. In healthy conditions, dental pulp is protected from microorganisms of the oral cavity by enamel and dentin. The exposure of dental pulp to microorganisms as a consequence of dental caries, fractures or operative procedures triggers a local inflammatory response. The progression of such infection and inflammation results in necrosis of the pulp and involvement of periapical tissues, generating a PL (Nair, 1997). An initial acute inflammatory response induces tissue changes in the apical region, such as hyperemia and neutrophil recruitment, which can shift to the formation of a granulation tissue with chronic inflammatory cells and fibroblasts, the apical granuloma. A granuloma can remain latent or be converted to an epithelium lined cavity, the inflammatory cysts. These pathological changes in periapical tissues are the clinical consequence of the host defensive reaction against bacterial products that egress through apical foramen from infected dental pulp (Nair, 1997), but inhibition of this inflammation tends to aggravate the formation of osteolytic lesions through impairment of the antibacterial activity of the host response, that is critical in endodontic lesions (Graves et al., 2000). Similarly to PD, this response is characterized by the persistent release of inflammatory mediators, such as chemokines and cytokines (Kawashima et al., 2007, Nair, 1997, Silva et al., 2007, Queiroz-Junior et al., 2011, Vernal et al., 2006), and migration of inflammatory cells (Liapatas et al., 2003, Stashenko et al., 1992) to infected sites (as stated in Table 1). It largely prevents microbial invasion into periapical tissues (Liapatas et al. 2003, Nair, 1997), but it also induces the resorption of the periapical alveolar bone (Stashenko et al., 1992). Although the commitment of immune cells and production of inflammatory mediators protect the host from pathogen invasion, it also accounts for periapical bone resorption (Nair, 1997, Takahashi, 1998).

Cytokine / Chemokine	Cellular Source	Receptor	Function	Levels in		Reference
				Homeostasis	Inflammation	
IL-1β	Phagocytes (Neutrophils, Macrophages) Epithelial cells Fibroblasts	IL-1R1 IL-1R2	Induces inflammatory cell migration Induces bone resorption	Absent or low	Increased in chronic inflammation	Bloemen et al., 2010
IL-4	Th2 cells	IL-4R	Prototypical Th2 cytokine Anti-inflammatory properties Induces IL-10 production B cell stimulatory factor Humoral immune response Suppressing the polarization of Th1 cells Inhibit the transcription of pro-inflammatory cytokines Inhibits production of MMPs and RANKL Induces the upregulation of its respective inhibitors TIMPs and OPG	Absent or low	Low to high, depending on the nature of inflammatory immune response	Cronstein, 2007 Kawashima et al., 1999 Fukada et al., 2009 Ihn et al., 2002 Pestka et al., 2004 Agnello et al., 2003, Appay et al., 2008, Bluestone et al., 2009
IL-6	Phagocytes (Neutrophils, Macrophages) T and B cells Epithelial cells	IL-6R	Osteoclastogenesis processes Promotes bone resorption Pro-inflammatory properties	Absent or low	Increased in chronic inflammation	Pestka et al., 2004 Cronstein, 2007

Cytokine / Chemokine	Cellular Source	Receptor	Function	Levels in		Reference
				Homeostasis	Inflammation	
	Fibroblasts Osteoblasts		Inflammatory cell migration Humoral immune response			
IL-9	Th2 cells	IL-9R	Promotes allergic inflammation associated with various Th2 responses Promotes Th17 cells development Increasing the activity of Treg cells	Absent or low	Low to high, depending on the nature of inflammatory immune response	Hauber et al., 2009 Elyaman et al., 2009, Novak et al., 2009
IL-10	Th2 cells Treg cells	IL-10R1 IL-10R2	Anti-inflammatory properties Protective role in tissue destruction Stimulates OPG production	Absent or low	Increased	Pestka et al., 2004 Chou et al., 2006 Zhang & Teng, 2006
IL-12	Monocytes/ Macrophages Dendritic cells	IL-12Rβ1 IL-12Rβ2	Mediates alveolar bone resorption via IFN-γ Inhibits osteoclast activation *in vitro*	Absent or low	Low to high, depending on the nature of inflammatory immune response	Sasaki et al., 2008 Queiroz-Junior et al., 2010
IL-17	T cells Th17 cells Mast cells	IL-17RA/ IL-17R IL-17RB/ IL-15R IL-17RC IL-17RD/ SEF IL-17RE	Osteoclastogenic properties Upregulates IL-1β and TNF-α Inducer of RANKL production Neutrophil mobilization	Absent or low	Low to high, depending on the nature of inflammatory immune response	Yago et al., 2009 Kotake et al., 1999 Sato et al.,2006 Yu et al., 2007
IL-22	T cells Dendritic cells	IL-22Rα1	Anti-inflammatory properties Positively correlated to OPG, IL-10 and TGF-β Participates in adaptive response	Absent or low	Low to high, depending on the nature of inflammatory immune response	Brand et al., 2006 Valencial et al., 2006
TNF-α	Phagocytes (Neutrophils, Macrophages) Epithelial cells Fibroblasts	TNFR1 TNFR2	Upregulates adhesion molecules Upregulates chemokine production Regulates production of IL-1β and IL-6 Induces cell migration Increases of MMPs and RANKL expression	Absent or low	Increased in chronic inflammation	Dinarello, 2000 Kindle et al., 2006 Garlet et al., 2007a Wajant et al., 2003 Graves, 2008 Peschon et al., 1998
TGF-β	Treg cells Monocytes/ Macrophages	TGF-βRI TGF-βRII	Pleiotropic cytokine Regulates cell growth Regulates differentiation and matrix production Potent immunosuppressive factor Downregulates IL-1β, TNF-α, MMPs production	Increased	Low to high, depending on the nature of inflammatory immune response	Cardoso et al., 2008 Okada & Murakami, 1998 Steinsvoll et al., 1999 Dutzan,

Cytokine / Chemokine	Cellular Source	Receptor	Function	Levels in		Reference
				Homeostasis	Inflammation	
			Protective role against tissue destruction			2009a, Dutzan, 2009b Appay et al., 2008 Murphy & Reiner, 2002
IFN-γ	Th1 cells NK cells		Induces inflammatory cytokines Induces chemokines Stimulates osteoclast formation Main phagocyte-activating cytokine bone loss described by in vivo inhibit osteoclastogenesis in vitro	Absent or low	Low to high, depending on the nature of inflammatory immune response	Garlet et al., 2008 Sallusto and Lanzavecchia, 2011, Schroder et al., 2004 Repeke et al., 2010 Ji et al., 2009, Takayanagi et al., 2005
CXCL8 (IL-8)	Phagocytes (Neutrophils/ Polymorphonuclear leukocytes Monocytes/ Macrophages) Lymphocytes, Mast cells Epithelial cells Fibroblasts Endothelial cells, Osteoclasts.	CXCR1	Inflammatory chemokine Neutrophil chemotaxis activating factor (Enhances production of Leucotrien B4) Induces osteoclast differentiation and activity	Absent or low	Increased	Yoshimura et al., 1987 Tonetti et al., 1998 Darveau, 2010 Rossi, 2003 Traves & Donnelly, 2005 Bendre et al., 2003
CCL2 (MCP-1)	Phagocytes (Neutrophils/ Polymorphonuclear leukocytes Monocytes/ Macrophages) Lymphocytes, Mast cells Epithelial cells Fibroblasts Endothelial cells, Osteoblasts Osteoclasts.	CCR2 CCR11	Chemoattracts monocytes Inflammatory bone remodeling Limits infiltration of PMNs Chemoattracts for osteoclast precursors	Absent or low	Increased	Koch et al., 1992 Bonecchi et al., 2009 Garlet et al., 2010
CCL3 (MIP-1α)	Phagocytes (Neutrophils/ Polymorphonuclear leukocytes Monocytes/	CCR1 CCR5	Chemotatic for lymphocytes, monocytes / macrophages, basophils, eosinophils, dendritic cells. Stimulates bone resorption Homologus chemokines	Absent or low	Increased	Koch et al., 2005 Gemmel et al., 2001 Alnaeeli et al., 2007

Cytokine / Chemokine	Cellular Source	Receptor	Function	Levels in		Reference
				Homeostasis	Inflammation	
	Macrophages) Lymphocytes, Mast cells Epithelial cells Fibroblasts Endothelial cells, Osteoclasts.		CCL4 and CCl5			Taub, 1996 Repeke et al., 2010 Graves et al., 2011
CCL5 (RANTES)	Phagocytes (Neutrophils/ Polymorphon uclear leukocytes Monocytes/ Macrophages) Lymphocytes, Mast cells Epithelial cells Fibroblasts Endothelial cells, Osteoclasts.	CCR1 CCR5	Chemoattracts for lymphocytes, monocytes Induces CXCL8 and IL-6 production	Absent or low	Increased	Koch et al., 2005 Yu et al., 2004 Garlet et al., 2003 Gemmel et al., 2001 Gamonal et al., 2001 Nanki et al., 2001
MMPs	Phagocytes (Neutrophils/ Polymorphon uclear leukocytes Monocytes/ Macrophages) Lymphocytes Epithelial cells Fibroblasts Endothelial cells	TIMPs[1]	Remodeling of extracelleular matrix	Absent or low	Increased	Garlet, 2010 Garlet et al., 2006 Hannas et al., 2007 Verstappen and Von, 2006 Birkedal-Hansen, 1993
TIMPs		MMPs[1]	Regulates matrix remodeling	Low	Decreased or Increased	Garlet, 2010 Garlet et al., 2006 Hannas et al., 2007
RANKL	Osteoblasts[2] Osteocytes[2] Leukocytes[3]	RANK	Differentiation and activation of osteoclasts	Low	Increased	Teitelbaum, 200 Katagiri and Takahashi, 2002
OPG	T cells Osteoblasts	RANKL[1]	Inhibits bone resorption by preventing RANK-RANKL engagement	Low	Decreased or Increased	Teitelbaum, 2000 Katagiri and Takahashi, 2002

Notes:
1 – in the absence of a "receptor", the coupling molecules were listed
2 – under homeostatic conditions
3 – under inflammatory conditions

Table 1. Cytokines and chemokines involved in the pathophysiology of periodontal and periapical diseases

Therefore, the etiology of PD and PL shares the paradoxical condition in which the same host systems that provide protection against distinct pathogens are responsible for tissue destruction. Activation of these systems to achieve defense virtually always results in some degree of destruction which, if not controlled, will lead to tooth loss as the end result (Garlet, 2010, Nair, 1997, Page et al., 1997, Silva et al., 2007).

3. Periodontal and periapical tissues under homeostatic and inflammatory conditions

A normal periodontium is a complex and dynamic structure composed of soft and hard tissues, encompassed cementum and self-renewing tissues including the gingival mucosa (epithelium and connective), periodontal ligament, alveolar bone which, together, provide attachment apparatus for teeth into the jaw (Potempa et al., 2000, Bosshardt & Lang, 2005). The periodontal tissues are constantly exposed to multiple assaults by microbes that live harmoniously in the oral niche. The homeostasis of these tissues depends on a dynamic equilibrium of bacteria–host interactions. Besides the overall periodontal tissues, the pulp tissue, usually free of microbial challenge in healthy conditions, play an important role in the initial host responses that can lead to the development of PLs, and therefore will be also considered in the sequence.

3.1 Periodontal and pulpar tissues under homeostatic conditions

Gingival epithelium is the first line of host defense, represented not only by its barrier function that physically hamper microbial invasion in gingival sulcus and periodontal soft and mineralized connective tissues, but also by its antimicrobial properties that biologically suppress the propagation of putative pathogens (Darveau et al., 1997, Lu et al., 2004, Page et al., 1997). This epithelium adjacent to a tooth can be classified into three anatomical types: the oral gingival epithelium, the sulcular epithelium, and the junctional epithelium (Hatakeyama et al., 2006).

The oral gingival epithelium is composed of a keratinizing stratified epithelium and covers the external surface of the gingiva, while the sulcular epithelium is a nonkeratinizing epithelium that lines the inner aspect of the gingival sulcus. In contrast, the junctional epithelium is structurally and functionally unique. Namely, the junctional epithelium is located at a strategically important interface between the gingival sulcus and the underlying soft and mineralized connective tissues of the periodontium (Hatakeyama et al., 2006, Hormia et al., 2001), contains a nonkeratinizing epithelial layer at the free surface. The gingival epithelium, in particular, the junctional epithelium is highly porous and the epithelial cells are interconnected by a few desmosomes and the occasional gap junction, resulting in wider intercellular spaces that may provide a pathway for fluid and transmigrating leukocytes from the gingival connective tissue to the gingival sulcus (Hashimoto et al., 1986, Bosshardt & Lang 2005, Hatakeyama et al., 2006), and even for microorganisms moving in the opposite direction (Bosshardt & Lang 2005, Darveau, 2010, Darveau et al., 1997, Marra & Isberg, 1996, Page & Schroeder, 1976, Tonetti et al., 1998). In the absence of clinical signs of inflammation, approximately 30,000 polymorphonuclear leukocytes (PMNs) migrate *per* minute through the junctional epithelia of all human teeth into the oral cavity (Darveau, 2010, Schiött & Löe, 1970). The tissue fluid transports a variety of molecules through the junctional epithelium to the bottom of the gingival sulcus. These molecules, together with the leukocytes, represent a host defense system against the

bacterial challenge. Its interposition between the underlying soft and mineralized connective tissues of the periodontium points to its important roles in tissue homeostasis and defense against micro-organisms and their products (Schroeder & Listgarten, 1997). Moreover, the highly dynamic nature of the junctional epithelium indicates an important role for the cells themselves in the maintenance of tissue integrity, being essential for its protective and regenerative functions (Schiött & Löe, 1970).

In health condition, the connective tissue components are subject to a tightly controlled cycle of synthesis and breakdown (Potempa et al., 2000). At clinically healthy sites, a balanced and dynamic equilibrium challenge of bacteria–host may be beneficial, resulting in resistance to colonization by periodontopathogens and triggering other less-well-defined responses of the host. By contrast, this delicate balance in connective tissue turnover continuously challenged by the accumulation of bacteria on the tooth surface, if excessive, can ignite an inflammatory reaction aimed to eradicate the microbial intruders. Although indispensable for host defense against pathogens, this response may upset homeostasis within the periodontium, leading first to gingivitis and then to periodontitis (Bosshardt & Lang, 2005, Potempa et al., 2000), as will be described in the sequence. In addition, the extracellular matrix (ECM) and collagen type I of the connective tissue help stabilize periodontal tissues, and fibronectins affect cell morphology, migration and differentiation (Darveau, 2010, Mussig et al., 2005). The coordinated regulation of cell proliferation and differentiation events is controlled by host signaling mechanisms and is referred to as tissue homeostasis. These signaling mechanisms maintain homeostasis of the periodontal tissue by regulating epithelial cell functions as well as connective-tissue resident cells and hematopoietic cells (Darveau, 2010).

Among the host proteases that target the ECM, the matrix metalloproteinases (MMPs) have been especially associated with the remodeling of periodontal tissues (Garlet, 2010, Garlet et al., 2006, Hannas et al., 2007, Verstappen & Von den Hoff, 2006) during different physiological and pathological processes (Birkedal-Hansen, 1993, Garlet, 2010, Garlet et al., 2006). MMPs, a family of zinc- and calcium-dependent proteases, are usually found in balance with a group of endogenous proteins named tissue inhibitors of metalloproteinases (TIMPs), to keep matrix remodeling highly regulated (Garlet, 2010, Garlet et al., 2006, Hannas et al., 2007). In fact, MMPs and TIMPs are regularly expressed in healthy periodontal tissues, where they are supposed to control the ECM physiological turnover (Garlet et al., 2006, Gonçalves et al., 2008). It is thought that MMPs and TIMPs are involved in the physiological turnover of periodontal tissues, and MMPs appear to be involved in tissue destruction in PDs (Birkedal-Hansen, 1993, Garlet et al., 2006, Golub et al., 2001, Reynolds et al., 1994, Van der Zee et al., 1997). However, there are contradictory results regarding the balance of MMPs/TIMPs in pathological versus healthy gingival samples (Aiba et al., 1996, Dahan et al., 2001, Garlet et al., 2006, Garlet et al., 2004, Ingman et al., 1996, Kubota et al., 1996, Nomura et al., 1998). Some studies show a decrease in the levels of TIMPs in diseased periodontal tissues, supporting the idea that an imbalance in the levels of TIMPs/MMPs occurs in PDs and results in tissue destruction (Garlet et al., 2006, Soell et al., 2002, Tuter et al., 2002). Conversely, other studies detected an increased expression of TIMPs in diseased periodontal tissues (Alpagot et al., 2001, Garlet et al., 2006, Garlet et al., 2004, Haerian et al., 1995, Nomura et al., 1998) which could reflect an attempt to maintain the tissue homeostasis, in view of the increased expression of MMPs. However, such up-regulation of TIMPs may not be enough to compensate for the even higher upregulation of MMPs, and such an imbalance may result in periodontal destruction. Nevertheless,

imbalances in the MMP/TIMP system (i.e. lower levels of TIMPs and/or higher levels of MMPs) are involved in the pathogenesis of several diseases including rheumatoid arthritis (Garlet et al., 2006, Katrib et al., 2003, Lanchou et al., 2003, Romas et al., 2002, Schulze et al., 2003, Yoshihara et al., 2000), which share several features with PDs, including the chronic nature of the inflammatory reaction and tissue destruction (Garlet et al., 2006, Mercado et al., 2003).

In the soft tissues context, it is also important to consider the features that characterize the dental pulp. The dental pulp consists of a connective tissue with a complex and rich neuronal and vascular networks surrounded by dentin walls, which lacks epithelium, differing from others connective tissues (Goldberg et al., 2004, Shroder, 1985). The pulp tissue is composed by heterogeneous cell populations responsible for its maintenance, defense, and repair. The cell types identified within the pulp include fibroblasts, which are the predominant cell type, as well as inflammatory and immune system cells, including dendritic cells, neutrophils, histiocytes/macrophages, T-/B- lymphocytes and odontoblasts (Izumi et al., 1995). Several niche environments for latent or dormant pulpal stem cells (progenitors), necessary for repair and regenerative processes, have been identified within the components of dental pulp (Huang et al., 2009, Shi et al., 2003, Sloan et al., 2007). Interestingly, while periodontal tissues are directly exposed to a microbial challenge even both health and disease conditions, dental pulp features comprise a special situation where the tissue is enclosed by a rigid, mineralized tissue shell, and thus the microbial challenge only will reach the host tissue after significant enamel and dentin matrix degradation, or in other words, in already established pathological process. While the mineralized structure may present an initial protective role, in the course of pathological process the tubular structure of dentin confers significant permeability properties on the tissue (Pashley et al., 2002) and bacterial products may diffuse down the dentinal tubules and invoke cellular responses (Bergenholtz, 1990, Smith et al., 2001). After dental tissue damage by caries lesions, odontoblasts are the first pulp cells to encounter both products of the infectious process, including the invading pathogens and their components, as well as detecting dentine matrix constituents released during demineralization. Although odontoblasts provide barrier function by protecting the underlying tissue from the invading bacteria, they are also immunocompetent and capable of coordinating an inflammatory response (Veerayutthwilai et al., 2007). Progression of the carious infection deeper into the underlying dental tissue results in changes in the composition of the bacterial biofilm (Takahashi et al., 2008) and also deleterious effects on the host cells, including death of pulp cells. Certainly, further molecular interactions between bacteria and stem cells at the core of the pulp arise, resulting in exacerbation of inflammatory events.

Finally, it is important to consider the structure and properties of the periodontal ligament (PDL), which is responsible for supporting the teeth and can be affected by inflammatory conditions of periodontal and pulpar origin. The PDL is critical for teeth positioning within the alveolar bone and for absorbing forces generated by chewing. The main components of the PDL are blood vessels, fibroblasts, and collagen fibers, composed primarily of collagen type I. Several previous studies have demonstrated that mesenchymal stem cells associated with the vasculature within the PDL have the potential to differentiate into cell types that populate bone and cementum (McCulloch & Bordin, 1991, Trombetta & Bradshaw, 2010). Thereby, resident cells of the PDL are postulated to play an important role in periodontal health and disease by providing cellular source for regeneration of the primary tissues injured in PD. It is because of their ability to proliferate, migrate and synthesize several

components of the periodontium, and also participate in both protective and destructive mechanism that prevents periodontitis or impede its progression, and initiates lesions and promotes progressive disease by various biological mechanisms, respectively (Benatti et al., 2009, Gemmell & Seymour, 2004).

PDLC (periodontal ligament cells) proliferation is considered one of the major events for periodontal homeostasis, because of their capacity to proliferate and differentiate into all the other periodontal tissues (Benatti et al., 2009). Another key event critical for periodontal tissue homeostasis in which PDLC play a significant role is the bone remodeling process. PDLC play a major role in alveolar bone metabolism in periodontal health and disease, because of their ability to secrete factors that regulate the homeostasis of connective and osseous tissue, including inflammatory cytokines such as interleukins (ILs), and the major osteoclast regulators receptor activator of nuclear factor-kB ligand (RANKL) and osteoprotegerin (OPG) (Ogasawara et al., 2004, Benatti et al., 2009).

In addition to the soft connective tissue elements, alveolar bone loss is a key structure of periodontal and periapical environments. Bone homeostasis depends on the maintenance of a delicate equilibrium between bone resorption by osteoclasts and bone formation by osteoblasts. The major mechanism that regulates bone remodeling is driven by the receptor RANK (receptor activator of nuclear factor-κB, also known as TNFRSF11A), its ligand RANKL (also known as TNFSF11), and its soluble counterpart OPG (also known as TNFRSF11B) (Boyle et al., 2003, Cochran, 2008, Darveau, 2010, Garlet, 2010, Leibbrandt & Penninger, 2008, Nagasawa et al., 2007). RANKL binding to the receptor RANK, present on the surfaces of pre-osteoclasts, drives their maturation and activation, while OPG acts as a decoy receptor and inhibits RANK-RANKL engagement (Leibbrandt & Penninger, 2008). Therefore, the balance between RANKL and OPG expression is essential for bone remodeling, but the expression of such system is usually investigated in the viewpoint of pathological changes (Baud'huin et al., 2007, Garlet, 2010, Garlet et al., 2006, Menezes et al., 2008, Rodan & Martin, 2000, Romas et al., 2002), and the exact participation of such mediators in homeostatic bone remodeling of alveolar bone remain unclear.

It is important to make clear that tissue homeostasis represents a delicate balance between anabolic and catabolic activities, and that a wide range of stimuli can disrupt this balance and compromise the tissue integrity. Along such stimuli, inflammation-related molecules can result in pathological changes in periodontal, periapical and pulpar tissues, as discussed in the next section. However, it is important to consider that even in clinical health conditions, the periodontium continuously expresses cytokines, chemokines and cell adhesion molecules, associated with a basal level of inflammation, thought to be responsible for providing protection against bacterial challenge without resulting in tissue damage. Indeed, as previously cited, periodontal tissues are directly exposed to a microbial challenge even in healthy subjects. To cope with such microbial stimulation, the periodontium has a highly orchestrated expression of select innate host defence mediators (Darveau, 2010). Periodontal tissue, unlike the intestine, does not have a large mucous layer to prevent contact between the microbial community and the epithelial cell surface (Bosshardt & Lang, 2005, Darveau, 2010). In fact, although both periodontal and intestinal tissues are in close proximity to polymicrobial communities, it seems that they use two completely different strategies to contend with the constant presence of microbial stimulation. The intestinal epithelium is a single layer of cells connected by tight junctions that channels bacteria and their components to the highly specialized Peyers patches, where a localized, fully developed lamina propria can recognize microorganisms and respond accordingly

(Darveau, 2010, Duerkop et al., 2009). Like the intestinal epithelium, clinically healthy human gingival tissue expresses a wide range of toll-like receptors (TLRs), including TLR1–TLR9 (Darveau, 2010, Mahanonda & Pichyangkul, 2007, Ren et al., 2005, Sugawara et al., 2006,). Innate host protective mechanisms are coupled with regenerative and biomechanical signalling systems, resulting in tissue homeostasis. The status of healthy periodontal tissue results in the coordinated expression of E-selectin, intercellular adhesion molecules (ICAMs) and interleukin-8 (IL-8) which facilitates neutrophil transit through the tissue, where they form a wall between the host tissue and the dental-plaque biofilm (Tonetti et al., 1998, Darveau, 2010). Interestingly, some cytokines usually associated with chronic inflammation and tissue damage, such as IL-1, IL-6, TNF-α, are found in gingival crevicular fluid from clinically healthy sites, but in lower levels than in diseased sites. In this context, the transition from a healthy-related to a disease-related inflammatory condition seems to be associated with quantitative and qualitative changes in the host inflammatory immune response, whose characteristics have been investigated usually in a pathological context, which will be discussed in the sequence.

3.2 Periodontal and periapical tissues under inflammatory conditions – Pathways involved in tissue destruction

Cytokines play a major role in inflammatory and immune responses within the bone microenvironment. The balance between pro- and anti-inflammatory mediators determines the outcome of resorption in bone destructive diseases, as in periodontitis (Garlet et al., 2006, Menezes et al., 2008) and periapical granulomas (Silva et al., 2005, Silva et al., 2007) (Table 1). However, before specific discussion on host response to periodontal and periapical diseases outcome modulation, it is important to review the molecular pathways associated with periodontal and periapical tissues destruction. As previously considered, MMPs have been associated with remodeling of the periodontal tissues with special interest (Hannas et al., 2007, Shin et al., 2002, Verstappen & von den Hoff, 2006), and are usually found in balance with TIMPs in order to keep matrix remodeling in a highly regulated fashion (Hannas et al., 2007). However, unbalanced MMPs/TIMPs ratio was described in diseased periodontal and periapical tissues, and is thought to account for the soft and mineralized tissue destruction associated to periodontal and periapical diseases (Garlet et al., 2004, Gonçalves et al., 2008, Shin et al., 2002, Verstappen & von den Hoff, 2006). In accordance, the disarray of the MMPs/TIMPs model is involved in the pathogenesis of osteolytic diseases (Malemud, 2006), and the MMPs inhibition is proposed as an adjuvant therapy to control PD (Giannobile, 2008).

Besides the connective tissue destruction, alveolar bone loss is a key event in bone inflammatory diseases, as in periodontitis and chronic PLs. The integrity of bone tissues depends on the maintenance of a delicate equilibrium between osteoclasts and osteoblasts. It has been proposed that proinflammatory cytokines play a fundamental role in periapical bone destruction through the induction of RANKL, while OPG synthesis is supposed to attenuate lesion progression (Garlet et al., 2006, Menezes et al., 2008). As previously cited, the major regulatory mechanism of osteoclasts activity is driven by the receptor RANK, its ligand RANKL and its soluble counterpart OPG (Leibbrandt & Penninger, 2008). Being the balance between RANKL and OPG expression essential to determine the overall bone loss outcome. Regarding periodontal and periapical diseases, an increased RANKL expression in diseased periodontal and periapical tissues are described (Cochran, 2008, Garlet et al., 2004).

Interestingly, the patterns of RANKL/OPG expression present a high variation between inactive PD (i.e. chronic gingivitis) and active PLs (i.e. periapical granulomas) (Menezes et al., 2008) and also significantly differ between clinical forms of periodontitis (i.e. aggressive versus chronic periodontitis) (Garlet et al., 2004). For that reason, it is possible that RANKL/OPG balance may be associated with the stable or progressive nature of periodontal lesions. Previous human studies showed that RANKL/OPG balance was associated with osteolytic activity and the experimental disease progression (Garlet et al., 2006). Accordingly, the blockade of RANKL by OPG leads to a reduction of alveolar bone loss throughout experimental PD in mice (Jin et al., 2007). Appropriately, the coupled bone formation, which takes place under homeostatic conditions (Parfitt, 1982), seems to contribute to the conventional increased bone resorption in overall bone loss in PD (Behl et al., 2008). It has long been assumed that the host defense against microbial invasion and subsequent tissue destruction involves both innate and adaptive immunity cytokines. We are going to discuss both immune response mechanisms, separately, in this chapter.

4. Classic inflammatory cytokines role in periodontal and periapical inflammatory lesions

As previously discussed in this chapter, the presence of pathogens is required, but not sufficient for bone inflammatory diseases initiation, being the host response a critical determinant of periodontal and periapical tissues breakdown (Graves, 2008, Nair, 2004). The innate host response initially involves the recognition of microbial components as "danger signals" by host cells and the subsequent production of inflammatory mediators. The TLRs are expressed by resident cells and leukocytes in periodontal habitat, and activate the innate immune response, binding to various bacterial components (i.e., LPS, bacterial DNA, diacyl lipopeptides, peptidoglycan, etc) (Mahanonda & Pichyangkul, 2007). TLR-2 and TLR-4 seem to participate in the recognition of periodontopathogens such as *A. actinomycetemcomitans, P. gingivalis and T. forsythia* (Nussbaum et al., 2009). After TLRs activation, an intracellular signaling cascade is initiated. This signalling cascade involves activation of transcription factors and the subsequent inflammatory cytokines expression, leukocyte migration and osteoclastogenesis (Lima et al., 2010, Nakamura et al., 2008, Ukai et al., 2008). In accordance, the absence of TLR2 or TLR4 results in reduction of alveolar bone loss in mice after *P. gingivalis* infection (Costalonga et al., 2009, Lima et al., 2010, Nakamura et al., 2008). Besides TLRs, the nucleotide-binding oligomerization domain (NOD) receptors and the inflammasome system have been described as potential accessory molecules in triggering innate host response against periodontal pathogens (Okugawa & Bostanci, 2009, Uehara & Takada, 2007). The first mediators to have their role related to PD pathogenesis were innate immunity cytokines produced after microbial recognition, such as TNF-α, IL-1 and IL-6. These cytokines are produced by both resident cells (i.e. epithelial cells and fibroblasts) and phagocytes (i.e. neutrophils and macrophages) in periodontal environment. While the exact contribution of each cell type remains to be elucidated, previous studies described that a hyper-reactive phenotype of phagocytes is related to increased pro-inflammatory cytokines production in both aggressive and chronic PD (Gustafsson et al., 2006, Shaddox et al., 2010). Recent evidence also points to important roles of resident cells in periodontal bone loss, since the periodontal ligament fibroblasts and osteoclast precursors contact synergistically

increases the expression of genes related to osteoclastogenesis, such as RANKL, TNF-α and IL-1 (Bloemen et al., 2010).

TNF-α is responsible for cell migration process at multiple levels, inducing the upregulation of adhesion molecules and the production of chemokines, which are chemotactic cytokines involved in cell migration to infected and inflamed sites (Dinarello, 2000, Kindle et al., 2006, Peschon et al., 1998, Wajant et al., 2003). TNF-α is present at high levels in gingival crevicular fluid (GCF), diseased periodontal tissues (Garlet et al., 2004, Graves, 2008, Graves & Cochran, 2003), and radicular cysts (Teixeira-Salum et al., 2010), it is positively correlated with MMPs and RANKL expression. Supporting the data from human studies, experimental PD in rats and primates clearly demonstrated that TNF-α plays a central role in the inflammatory reaction, alveolar bone resorption and in the loss of connective tissue attachment (Graves, 2008, Graves & Cochran, 2003). Accordingly, experimental periodontitis in TNF-α p55 receptor deficient mice (TNFp55KO) was characterized by a significant decrease in MMPs and RANKL expression, which was associated with a significant decrease in the alveolar bone loss (Garlet et al., 2007a).

However, recent studies from mouse models point to important roles of cytokines in the control of periodontal infection. While the destructive roles of TNF-α in periodontal environment led to the proposal of anti-TNF therapies to control PD (Mayer et al, 2009), it was also demonstrated a dual role for TNF-α in the pathogenesis of experimental PD, since this cytokine present an important role in the control of experimental *A. actinomycetemcomitans* infection, as demonstrated by the increased bacterial load and acute phase response presented by TNFp55-KO infected mice (Garlet et al., 2007a). Accordingly, TNFp55-KO mice characteristically present severe pathogen clearance impairment (Pfeffer et al., 1993). Besides its role in inflammatory cell migration previously cited, TNF-α plays a critical role in both innate and adaptive immune responses, upregulating antigen presentation and the bactericidal activity of phagocytes (Dinarello, 2000).

Besides the direct effect on the pathogenesis of periodontal and periapical diseases, TNF-α upregulates the production of other classic pro-inflammatory innate immune cytokines, such as IL-1β and IL-6 (Dinarello, 2000, Garlet et al., 2007a, Graves, 2008, Okada & Murakami, 1998, Wajant et al., 2003,). IL-1β and IL-6 have also been characteristically associated with inflammatory cell migration and osteoclastogenesis processes (Graves, 2008, Fonseca et al., 2009). Curiously, the individual absence of innate immunity cytokines attenuates inflammatory bone loss; however their simultaneous inhibition results in more effective protection leading to almost complete remission of bone loss rate (Sartori et al., 2009, Graves & Cochran, 2003).

In addition to a direct action toward bone resorption, innate immune cytokines also interfere with the coupled bone formation process (Behl et al., 2008). In fact, recent studies confirmed the early hypothesis that proinflammatory cytokines inhibit osteogenic differentiation (Ding et al., 2009, Lacey et al., 2009), and also demonstrate that activation of TLRs in osteoblasts induces the production of osteoclastogenic cytokines (Bar-Shavit, 2008).

5. T helper cytokines role in periodontal and periapical inflammatory lesions

Complementarily to the innate immune response, periodontal and endodontic bacteria result in mobilization of adaptive immunity mechanisms. The host adaptive response starts

with the recognition of the putative pathogens (using a similar set of TLRs and NODs as described to innate immunity cells) by antigen presenting cells, such as dendritic cells (Cutler & Jotwani, 2004). After activation, mature dendritic cells express co-stimulatory molecules and produce distinct patterns of cytokines that will determine the subsequent polarization and activation of antigen specific lymphocytes (Cutler & Jotwani, 2004). The immune response polarization is determined by prototypical cytokines of each pattern, and also involves the selective migration of CD4 T helper subsets and the subsequent production of characteristic cytokines at the response foci (Bluestone et al., 2009, Kalinski & Moser, 2005, Murphy & Reiner, 2002).

It has long been assumed that the pathogenesis of inflammatory diseases is mainly mediated by CD4 T cells subsets, Th1 and Th2 cells, contrasting in their pattern of cytokine production (Brand et al., 2006, Colic et al., 2007, Gaffen & Hajishengallis, 2008, Murphy & Reiner, 2002, Stashenko et al., 2008). As a general rule, immune responses mediated by T cells polarized into a Th1-type phenotype are characteristically cellular and pro-inflammatory, while Th2 cells are associated with humoral immunity and present anti-inflammatory properties (Jankovic et al., 2001, Murphy & Reiner, 2002). This has been supported by increased levels of Th1 cytokines (IFN-γ, IL-12) in bone destruction involved in the progression of chronic periapical and periodontitis diseases (Kawashima et al., 1999, Trombone et al., 2010). Under normal condition, proinflammatory mechanisms must be controlled in order to prevent excessive tissue destruction and promote autoimmune processes. Th2 cytokines (IL-4, IL-10) are classic antagonist of Th1 responses and associated to the humoral immune response and antibody production, leading to the restriction of inflammatory/immune mechanisms (Kawashima et al., 1999, Fukada et al., 2009).

IFN-γ is the signature cytokine of Th1-type responses, being considered the main phagocyte-activating cytokine and characteristically associated with the production of inflammatory cytokines and chemokines (Appay et al., 2008, Murphy & Reiner, 2002, Sallusto & Lanzavecchia, 2011, Schroder et al., 2004). Concerning periapical diseases of endodontic origin and periodontitis, IFN-γ is present at high levels in chronic PLs, and is associated with progressive lesions or higher severity (Colic et al., 2006, Colic et al., 2009, Dutzan et al., 2009, Garlet et al., 2003, Honda et al., 2006). In agreement, studies in rodents demonstrated that IFN-γ is involved in the development of inflammatory reaction and bone resorption in response to *A. actinomycetemcomitans and P. gingivalis* (Baker et al., 1999, Garlet et al., 2008, Teng et al., 2005). Interestingly, a controversial role for IFN-γ in bone lytic lesions have been described, since the association with increased bone loss described *in vivo* (human and experimental) is not confirmed by *in vitro* experiments, in which IFN-γ is described to systematically inhibit osteoclastogenesis (Ji et al., 2009, Takayanagi et al., 2005). In fact, *in vitro* data clearly demonstrated that IFN-γ induces rapid degradation of the RANK adapter protein TRAF6 by the ubiquitin-proteasome system, resulting in the inhibition of the RANKL-signaling and its subsequent osteoclastogenic events (Takayanagi et al., 2000). The *in vitro* data support a previous hypothesis that Th1 cells are associated with the stable lesions while Th2 cells are associated with disease progression (Gemmell et al., 2007). However, the pro-inflammatory effect of IFN-γ demonstrated *in vivo*, leading to the upregulation of TNF-α and IL-1β levels (and consequently RANKL) seems to overcome the direct anti-osteoclastogenic effect described *in vitro* (Gao et al., 2007, Garlet et al., 2008). In addition, IFN-γ also stimulates osteoclast formation and bone loss *in vivo* via antigen-driven T cell activation or through the chemoattraction of RANKL+ cells (Gao et al., 2007, Garlet et

al., 2008, Repeke et al., 2010). This finding is supported by a recent study, which demonstrates that Th1 cells (characterized as CD3+CCR5+CXCR3+ cells) are an important source of RANKL throughout experimental periodontitis (Repeke et al., 2010). An additional evidence of the adverse effect of Th1 response concerning periodontal tissue destruction indicates the role of IL-12 (the major Th1-inducing cytokine) mediating alveolar bone loss in mice after *P. gingivalis* challenge (Sasaki et al., 2008). However, as observed with IFN-γ, data from human periodontitis concerning the role of IL-12 in PD pathogenesis is controversial. Although studies demonstrate that IL-12 concentrations are lower within diseased than healthy gingival tissues (Johnson et al., 2005), a recent report showed that IL-12 levels decrease in gingival crevicular fluid following initial periodontal therapy (Thunell et al., 2009).

Meantime, similarly as described earlier to TNFp55-KO strain, IFN-γKO mice presented a severe impairment of protective immunity to *A. actinomycetemcomitans* infection, as demonstrated by the higher bacterial load in periodontium, increased acute phase response, and bacterial dissemination followed by mice death (Garlet, et al., 2008). The immune protection mediated by IFN-γ characteristically involves leukocyte recruitment and its subsequent activation at inflammatory foci (Schroder et al., 2004). Indeed, IFN-γ is considered the main phagocyte-activating cytokine by enhancing phagocytosis, antigen uptake and stimulating the production of inflammatory cytokines, chemokines and microbicidal molecules (Schroder et al., 2004). In fact, IFN-γ plays an essential role in clearing a wide range of infections (Schroder et al., 2004). As a result, further studies are required to determine the exact effect of Th1 cytokines, IFN-γ and IL-12, in the immunopathogenesis of periapical inflammatory diseases.

An extra possibility for a destructive role for T cells all over periodontitis and periapical diseases brings up the Th2 subset, also present in PDs and PLs (Gemmell & Seymour, 2004). Th2 cells commitment and action is primarily dependent of IL-4, the prototypical Th2 cytokine, which also acts as a B cell stimulatory factor (Appay et al., 2008, Murphy, 2002, Sallusto & Lanzavecchia, 2011). In addition to IL-4, IL-6 is further believed to contribute to B cell differentiation and antibody production (Cronstein, 2007). Previous studies demonstrated that B cells produce RANKL as a result of periodontal pathogens stimulation (Han et al., 2009), and also that the majority of B cells in periodontal lesions are RANKL+ (Kawai et al., 2006). Considering the hypothesis that B cells outnumber T cells in periodontal lesions, the predominance of a Th2-type response in periodontal lesions potentially leads to the accumulation RANKL producing cells and consequently to tissue destruction (Gemmell, 2002, Kawai et al., 2006). In fact, B cell deletion was recently demonstrated to prevent bone loss in mice after oral *P. gingivalis* infection (Baker et al., 2009). However, while B cells seem to contribute to alveolar bone loss, they are not essential since T cells are able to promote LPS-induced bone resorption in the absence of B cells (Yamaguchi et al., 2008). An additional possibility for a destructive role for Th2/B cell pole is the expression of autoantibodies against periodontal tissue components (such as collagen, heat shock proteins, vimentin, spectrin, filamin, actin, lamin, keratin, and tubulin), described in both aggressive and chronic PD patients (Koutouzis et al., 2009).

On the other hand, some studies propose that the Th2-type cytokine IL-4 may attenuate periodontitis progression, in contrast to its putative destructive role previously discussed. Although there is no evidence of the role of IL-4 in periapical diseases, this cytokine has been asssociated to control other inflammatory diseases, such as periodontitis and

rheumatoid arthritis (Bozkurt et al., 2006). IL-4 presents marked suppressive and anti-inflammatory properties mediated by its capacity to inhibit the transcription of pro-inflammatory cytokines and IFN-γ, then suppressing the polarization of Th1 cells (Agnello et al., 2003, Appay et al., 2008, Bluestone et al., 2009). Moreover, IL-4 induces the production of cytokines with similar or complementary suppressive properties, such as IL-10 (Pestka et al., 2004). In addition, IL-4 is also able to inhibit the production of MMPs and RANKL, and concomitantly induce the upregulation of its respective inhibitors TIMPs and OPG (Ihn et al., 2002), reinforcing its potential protective role in PD pathogenesis (Giannopoulou, 2003). Indeed, the concentration of IL-4 in GCF was demonstrated to decrease from periodontal health to disease, suggesting that this cytokine could mediate the remission or improvement of periodontal lesions (Bozkurt et al., 2006, Pradeep et al., 2009). The protective role for Th2-biased humoral immunity also refers to the prevention of alveolar bone loss after immunization protocols, which are usually associated with increase in serum immunoglobulin levels (Zhang, et al., 2009). Accordingly, a longitudinal human study demonstrated that serum levels of IgG antibodies against *A. actinomycetemcomitans* or *P. gingivalis* in periodontitis-stable patients were higher than those in patients with active periodontitis, suggesting a protective role for IgG (Rams et al., 2006).

Also in the tissue protection context, the prototypical anti-inflammatory cytokine IL-10 (Pestka et al., 2004) described to be widely expressed in inflamed periodontal and periapical tissues, is thought to be associated with lower disease severity (Colic et al., 2010, Garlet et al., 2006, Garlet et al., 2004, Rossi et al., 2008). Genuinely, IL-10 knockout mouse is highly susceptible to *P. gingivalis*-induced alveolar bone loss (Sasaki et al., 2004), and great PLs may be developed, reinforcing the important role of IL-10 in the pathogenesis of experimentally induced pulp infection as endogenous suppressor of PL development (Rossi et al., 2008). Studies suggest that IL-10 can act on multiple ways to restrain periodontitis severity. The control of inflammatory signaling mediated by IL-10 may involve the inhibition of inflammatory mediators mRNA transcription after TLR or cytokine signaling (Yoshimura et al., 2003). This control can be exerted by the suppressors of cytokine signaling (SOCS), which act to attenuate signal transduction as part of a negative feedback loop to inhibit the response to subsequent stimuli (Yoshimura et al., 2007). Accordingly, a recent study demonstrates that the upregulation of SOCS expression after the challenge with DNA from PD-associated bacteria significantly suppressed the response to a subsequent bacterial challenge (Taubman et al., 2007). Aside from the suppression of innate immunity cytokines, IL-10 interferes directly with IFN-γ and IL-17 production by T cells, demonstrating a broad role for this immunoregulatory cytokine (Jovanovic et al., 1998, Naundorf et al., 2009). Hence, in PLs, a previous study demonstrated that macrophages are able to control periapical tissue and alveolar bone destruction by inhibiting the DC-mediated production of IFN-γ by CD4+ T cells and by augmenting the secretion of IL-10 (Colic et al., 2010). Therefore, it is possible that IL-10 may reduce the inflammatory signaling that leads to inflammatory and Th1 cytokine mRNA transcription, which in turn could downregulate downstream pathways under its influence (Hosokawa et al., 2009). In accordance, the expression of SOCS-1 and SOCS-3 is significantly higher in inactive versus active periodontal lesions (Garlet et al., 2006).

In addition to the control of inflammatory reaction, IL-10 also presents a direct protective role in tissue destruction, modulating both MMPs and RANK systems. IL-10 characteristically induces the upregulation of TIMPs, which are capable of inhibiting almost

every member of the MMP family in a non-specific way (Chou et al., 2006, Claudino et al., 2008, Garlet et al., 2004). In fact, increased TIMPs levels in periodontal and periapical tissues are thought to effectively counteract MMPs, and have been associated with the attenuation of disease severity (Garlet et al., 2004, Lin et al., 2002, Ramamurthy et al., 2005, Sato et al., 2009). Moreover, IL-10 stimulates the production of OPG, which consequently inhibits bone resorption by preventing RANK-RANKL engagement (Zhang & Teng, 2006). Concurring, IL-10 modulates the levels of both TIMPs and OPG *in vitro* and *in vivo* (Kumada et al., 2004, Liu et al., 2006, Zhang & Teng, 2006). IL-10 was also described to suppress osteoclastogenesis by selectively inhibiting calcium signaling downstream of RANK and by inhibiting transcription of the osteoclast co-stimulatory molecule triggering receptor expressed on myeloid cells 2 (TREM-2) (Park-Min et al., 2009). Indeed, IL-10 are thought to present a direct effect over bone formation, since the alveolar bone loss in the absence of IL-10 is associated with a reduced expression of osteoblast and osteocyte markers, independently of microbial, inflammatory or bone-resorptive pathways (Claudino et al., 2008).

Interestingly, IL-10 was initially considered to be produced by Th2 cells in periodontal and PLs, but the discovery of Tregs as an important IL-10-producing T helper subset resulted in an evaluation of such concept. Indeed, while the association of Th2 cells with inflammatory diseases outcome remains controversial, Tregs have been described as a protective T cell subset concerning the tissue damage in periodontal and periapical environment. Natural Tregs are CD4+CD25+ T cells that specifically regulate the activation, proliferation, and effector function of activated conventional T cells determining the outcome of several immunological settings, ranging from infectious diseases to immunopathology and autoimmunity (Appay et al., 2008, Belkaid et al., 2009, Sallusto & Lanzavecchia, 2009, Shevach et al., 2009). Tregs seem to be essential for the maintenance of peripheral tolerance and to control the immune response (Kotake et al., 2001), presenting a suppressive effect on osteoclasts differentiation (Zaiss et al., 2007) and controlling bone resorption (Zaiss et al., 2010). Tregs characteristically express as phenotypic markers the transcription factor forkhead box P3 (FOXp3), CD103, the glucocorticoid-inducible TNF receptor (GITR), the inhibitory molecule cytotoxic T-lymphocyte-associated molecule 4 (CTLA-4) and cell surface TGF-β1, among other surface molecules (Li & Flavell, 2008, Shevach et al., 2009). Regarding PD, immunohistological, flow-cytometry and molecular analysis characterized Tregs in periodontal tissues by the expression of its phenotypic markers (FOXp3, CTLA-4, IL-10, GITR, CD103 and CD45RO), demonstrating therefore its presence in periodontal environment (Nakajima et al., 2005, Cardoso et al., 2008). Similarly, the presence of CD4+ CD25hi Foxp3+ Tregs was also observed in PLs, which inhibited the proliferation of responder T-cells *in vitro*, at least in part, by stimulating the production of IL-10 (Colic et al., 2010). A recent study demonstrates that CD4+Foxp3+ cells migrate to periodontal tissues after experimental infection, while its inhibition resulted in increased alveolar bone loss and inflammatory cell migration (Garlet, 2010). Interestingly, recent data demonstrated that Tregs inhibition throughout *A. actinomycetemcomitans*-induced experimental periodontitis in mice does not compromise the control of infection (Garlet, 2010). This apparent inconsistency may rely on the uniqueness of PDs, as previously discussed regarding the characteristics of host response against the subgingival biofilm and to individual invasive periodontal pathogens, and the still unknown degree and nature of host response required to restrain the periodontal infection.

Besides IL-10, Tregs-associated cytokine TGF-β and the inhibitory molecule CTLA-4 are also supposed to attenuate PD progression (Cardoso et al., 2008). Regarding CTLA-4, this classic Tregs marker is expressed by leukocytes in diseased periodontium, and was found to be increased in CD4+ cells of periodontitis patients when compared to healthy subjects (Aoyagi et al., 2000, Orima et al., 1999). Additionally, CTLA-4 suppresses the proliferation of T cells in response to periodontopathogens (Aoyagi et al., 2000). TGF-β can also play important roles in the attenuation of inflammatory damage in periodontal tissues. TGF-β is a pleiotropic cytokine that regulates cell growth, differentiation and matrix production, and is a potent immunosuppressive factor that downregulates the transcription of pro-inflammatory factors (such as IL-1β and TNF-α) and MMPs (Okada & Murakami, 1998, Steinsvoll, et al., 1999). Moreover, in active periodontal lesions and stable granulomas, TGF-β levels are negatively correlated with RANKL levels, reinforcing its protective role against tissue destruction (Dutzan, 2009a, Dutzan, 2009b, Steinsvoll et al., 1999).

Subsequently to the discovery of Tregs subsets, the identification of a Th17 subset that present effector antagonic roles for Treg-suppressive cells (Appay et al., 2008, Cardoso et al., 2008, Garlet, 2010, Sallusto & Lanzavecchia, 2009, Weaver, & Hatton, 2009), had an immediate impact not only on the understanding of T-cell function and regulation, but also has encouraged many researchers to re-examine the dichotomic Th1/Th2 model in bone inflammatory disorders, such as periodontal and periapical diseases.

Th17 lymphocytes is an osteoclastogenic cell subset (Yago et al., 2009), characterized as an IL-17-producing CD4 T cell subset, which have been implicated in numerous autoimmune and inflammatory conditions (Annunziato et al., 2008, Colic et al., 2008, Colic et al., 2007, Gaffen and Hajishengallis, 2008, Sallusto & Lanzavecchia, 2009). Th17 cells develop through cytokine signals distinct from, and antagonized by, products of the Th1 and Th2 lineages (Appay et al., 2008, Dong et al., 2008, Sallusto & Lanzavecchia, 2009). Although IL-23 is important for the final differentiation of Th17 cells (Kastelein et al. 2007), it is not the only cytokine responsible for their development and activation, IL-1, IL-6 and TGF-β seem to be also involved (McGeachy and Cua, 2008). It has been reported that T cells are involved in the bone destruction via IL-17 production, which in their turn is described as an inducer of RANKL production (Kotake et al., 1999, Sato et al., 2006). While some studies suggest that IL-17 seems to be less potent as a direct MMP inducer than classic innate immunity cytokines, the ability of Th17 cells to produce IL-6 and to upregulate IL-1β and tumor necrosis factor-α (TNF-α) production may generate an inflammation amplification loop, with a consequent increase of MMPs and RANKL expression. Recent reports demonstrated the presence of IL-17, in periodontitis and chronic PLs (Cardoso et al., 2008, Colic et al., 2007, Takahashi et al, 2005, Vernal et al., 2005). In consequence, Th17 cells are thought to exacerbate inflammatory diseases by activating adjacent cells to produce inflammatory mediators, generating therefore a positive loop for inflammatory reaction amplification that leads to lesion exacerbation. In accordance, recent evidences demonstrate that the Th17/IL-17 axis, by itself or along with pro-inflammatory and Th1 cytokines, mobilize macrophages and neutrophils against extracellular and intracellular pathogens. IL-17 was described to play a role in neutrophil mobilization after *P. gingivalis* infection (Yu et al., 2007). Interestingly, experimental studies in rodents demonstrate the IL-17 deficient mice may present increased or decreased bone lesions in response to periodontal pathogens challenge (Oseko et al., 2009, Yu et al., 2007). However, we must consider that experimental periodontitis or PLs models may not reflect perfectly the chronic nature of human disease,

and that alveolar bone loss in aged mice is associated to an increased expression of IL-17A. Curiously, IL-17 was also recently described to increase TLR responsiveness in human gingival epithelial cells, suggesting that this cytokine can play a supporting role in the innate immunity sensing of pathogens and in the subsequent host response.

Recently, it has been shown the involvement of others cytokines and Th subsets than Th1, Th2, Tregs and Th17 in the complex process of inflammatory diseases development and progression (Brand et al., 2006, Cardoso et al., 2009, Colic et al., 2007, Colic et al., 2008, Gaffen et al., 2008, Seiderer et al., 2008). IL-9 has long been thought to be a Th2 cytokine, as it promotes allergic inflammation and is associated with various Th2 responses (Hauber et al., 2009). However, reports have described an IL-9-secreting population T cell, Th9 cells, which are differentiated in culture with a combination of TGF-β1 and IL-4 (Dardalhon et al., 2008). IL-9 has also been shown to promote Th17 cells development, while increasing the activity of Treg cells (Elyaman et al., 2009, Novak et al., 2009). In addition, Th22, a novel Th cell population characterized by IL-22 expression, was identified in epidermis of patients with skin inflammatory disorders (Brand et al., 2006). Although, unpublished data from our group suggests a anti-inflammatory function for IL-22, since IL-22 was positively correlated to OPG, IL-10 and TGF-β in chronic periapical granulomas, exhibiting anti-inflammatory properties, in accordance to other studies in intestinal inflammatory diseases (Valencial et al., 2006). The opposite result could reinforce the theory proposed that IL-22 presents bi-directional function (Seiderer & Brand, 2009). In Chron's disease, an intestinal inflammatory disease, IL-22 was capable at the same time to stimulate proinflammatory mediators expression and to mediate the intestinal barrier function. Based on opposite effects of IL-22, it can be suggested the Th22 participation in adaptative immune response in PLs.

At this point, it is possible to propose that the differential expression of T helper cytokines in periodontal and periapical tissues determine the PD and PLs outcome. However, the discovery of new T cell subsets lead to a more complex scenario regarding the role of cytokines in periapical inflammatory diseases pathogenesis. In fact, the Th1/Th2 and Th17/Tregs paradigms provided interesting frameworks, but further studies are still required to integrate them in a string theory to unravel the destructive and protective role of cytokines from the tissue destruction viewpoint. Although the lipid mediators do not fit in the classic definition of cytokines (usually comprising proteins, peptides or glycoproteins), they may modulate or be modulated by them. However, recent reports suggest that the concept of "protective and destructive" mediators in the control of periodontal and periapical infection is an obviously simplified model, and that cytokines may present dual and apparently conflicting protective or destructive roles. Hence, a different perspective is that the spatial orientation of the inflammatory infiltrate to the bone and the periodontal ligament is an important component of determining whether the destructive influence is reversible as in the case of gingivitis or irreversible as in the case of periodontitits and pulp necrosis (Graves et al., 2011).

6. Chemokines as determinants of host response nature

Leukocytes are an essential part of the host's inflammatory response and are fundamental to antibacterial defense (Bellingan, 2000, Kantarci et al., 2003, Nathan, 2006). Their chemotaxis can be induced by several inflammatory mediators, including IL-1 and TNF-α, which in turn induce the production of specific chemoattractants, the chemokines. Chemokines are a family of potent chemotatic cytokines that regulate the trafficking and recruitment of

leukocytes to distant sites of inflammation (Zlotnik & Yoshie, 2000). The fine tuning of the regulation of the chemokine system is essential for host homeostasis and defense, and its abnormal expression is often associated with pathological processes (Garin & Proudfoot, 2011). The first cytokine identified to have chemotactic activity was IL-8, which proved to be a selective neutrophil chemoattractant (Yoshimura et al., 1987). The discovery of IL-8 triggered the search for other chemokines, stimulating a search for new family members with considerable interest in mediators responsible for the selective recruitment and activation of all leukocyte subsets (Murphy et al., 2000, Silva et al., 2007, Ward et al., 1998). Today, several chemokines have been described and they can be subclassified into four groups, according to their structure and spacing of conserved cysteine residues present in their molecules, namely CXC, CC, C and CX_3C (Murphy et al., 2000, Rossi et al., 2000, Zlotnik & Yoshie, 2000). This relatively new classification system was introduced in 2000, in which chemokines were considered as chemokine ligands, and each chemokine has been assigned a designation of CXCL or CCL (Rossi et al., 2000, Bacon et al., 2002). These ligands mediated their effects via 7-transmembrane domain receptors comprising a subset of G protein–coupled receptors (GPCRs) (Zlotnik & Yoshie, 2000). There is a great deal of redundancy and binding promiscuity between chemokine ligands and their receptors because some chemokines can bind multiple receptor subtypes, and some receptors can bind multiple chemokines (Murphy et al., 2000). Although most chemokine receptors recognize more than one chemokine, they are almost always restricted to a single subclass. Thus, the nomenclature system is rooted by the chemokine subclass specificity of the receptor been referred to as CC chemokines receptor (CCR) and CXC chemokine receptor (CXCR) followed by a number (Bacon et al., 2002, Murphy et al., 2000). Engagement of chemokine receptors with their respective ligands affects leukocyte migration by regulation of cytoskeletal re-arrangement, integrin-dependent adhesion, as well as by the binding and detachment of cells from their substrate (Silva et al, 2007).

Among the mediators potentially involved in leukocyte migration to periodontal and periapical environment, chemokines have been investigated with special interest (Silva et al., 2007). Chemokines are found in gingival tissue and crevicular fluid and are produced by a number of cell types in the periodontium, such as fibroblasts, endothelial cells, macrophages, osteoclasts, epithelial cells, polymorphonuclear leukocytes, monocytes, lymphocytes, and mast cells and exert their effects locally in paracrine or autocrine fashion (Baggiolini, 2001, Traves & Donnelly, 2005). Some chemokines have important proinflammatory effects and are related to periodontal tissue destruction that involves the stimulation of bone resorption and induction of tissue damage. Chemokines can also affect the recruitment, differentiation, or fusion of precursor cells to form osteoclasts or enhance osteoclast survival (Pradeep et al., 2009, Silva et al., 2007). They could also interfere with PD by recruiting cells, such as neutrophils, which protect host against bacterial invasion (Graves et al., 2011, Kantarci et al., 2003).

CXCL8 (IL-8) is an inflammatory chemokine which functions mainly as a neutrophil chemoattractant and activating factor. CXCL8 is able to upregulate the expression of adhesion molecules on the surface of neutrophils, enhancing leukotriene B4 (LTB4) production, inducing neutrophil chemotaxis and increasing neutrophils adherence to endothelial and epithelial cells (Rossi, 2003, Traves & Donnelly, 2005). CXCL8 is found at higher levels in gingival crevicular fluid prior to clinical signs of inflammation (Graves et al., 2011). As PD seems to be related to the progression of the inflammatory process to deeper periodontal tissues, chemokines found in both gingival tissue and crevicular fluid may play

an important role on its pathogenesis. In this regard, subjects with a history of periodontitis have high levels of CXCL8 in gingival tissue and crevicular fluid and these levels are correlated with disease severity (Graves et al., 2011, Tsai et al., 1995). Moreover, CXCL8 has a direct effect on osteoclast differentiation and activity by signaling through the specific receptor, CXCR1 (Bendre et al., 2003). Analysis of the chemokines KC/CXCL1 (the analogue of the human CXCL8), in an experimental model of PD in mice, revealed their expression in diseased tissues, preferentially in the junctional epithelium, and their correlation with the migration of PMNs (Garlet et al., 2005). Furthermore, there was a significant increase in the expression of CXCL8 by epithelial cells from periapical granulomas, suggesting that those cells also could increase vascular permeability and leukocyte chemotaxis (Takeichi et al., 2008).

Other abundant chemokine expressed in the connective tissue subjacent to gingival epithelium is Macrophage Inflammatory Protein-1α (MIP-1α)/CCL3 (Gemmell et al., 2001). CCL3 chemoattracts a variety of cells, including lymphocytes, monocytes, basophils and eosinophils (Koch et al., 2005, Taub, 1996). It is a ligand for the receptors CCR1 and CCR5 and is associated with the recruitment of monocytes/macrophages and dendritic cells via CCR1, and lymphocytes polarized into the Th1 phenotype by CCR5 (Alnaeeli et al., 2007). Thus, CCL3 has a potential role in stimulating bone resorption through effects on macrophages and Th1 cells (Graves et al., 2011). The number of CCL3-positive cells increases in periodontal tissues with increasing severity of PD. On the other hand, the absence of CCL3 does not affect the development of experimental PD in mice, probably due to the presence of homologous chemokines CCL4 and CCL5 which share the receptors CCR1 and CCR5 with CCL3 and present a similar kinetics of expression than CCL3 (Repeke et al., 2010).

Regulated upon Activation Normal T-cell Expressed and Secreted (RANTES/CCL5) is found in greater levels in active periodontal lesions compared to inactive sites (Gamonal et al., 2001, Gemmell et al., 2001) and it chemoattracts lymphocytes and monocytes as well as other cell types (Koch et al., 2005, Schall et al., 1990). The involvement of CCL5 in periodontal bone resorption is supported by findings that it binds to CCR1 and/or CCR5 (Garlet et al., 2003), inducing chemotaxis and the formation of osteoclasts *in vitro* (Yu et al., 2004). Fibroblasts from patients with rheumatoid arthritis, which shares some inflammatory features with PD, produce CCL5 mRNA upon stimulation with TNF-α, IL-1, or IFN-γ (Koch et al., 2005, Volin et al., 1998) and this production of CCL5 can participate in cytokine networks by inducing the production of CXCL8 and IL-6 (Nanki et al., 2001). Nevertheless, findings in a model of PL implicated CCR5 as a negative regulator of bone resorption, as mice lacking CCR5 presented larger PL than wild-type mice (Rossi et al., 2008). Accordingly, an increased amount of orthodontic tooth movement, correlated with increased alveolar bone resorption, was observed in the absence of CCR5 in mice (Andrade Jr. et al., 2009). Interestingly, an intermediate phenotype of PD development was observed after individual blockage of CCR1 and CCR5 (using genetically deficient mice strains) (Repeke et al., 2010). Thus, supported by findings that showed CCR1 expression in pre-osteoclasts and its increase expression in RANKL differentiated osteoclasts (Yu et al., 2004), it seems that the bone resorptive activity of CCL5 in PD and PL might be mediated by its engagement with CCR1, while it seems to be controlled by CCR5, although lack direct evidence to support this hypothesis.

Monocyte chemoattractant protein-1 (MCP-1/CCL2) is a potent chemoattractant for monocytes (Koch et al., 1992), detectable in the sera of patients with rheumatoid arthritis

(Koch et al., 2005). CCL2 is produced by a variety of cell types, either constitutively or after induction by oxidative stress, cytokines, or growth factors (Yada et al., 2010). CCL2 binds to CCR2 and CCR11 receptors, however, binding to CCR11 does not result in increased intracellular calcium mobilization, which is essential for chemotaxis (Schweickart et al., 2000). Some evidence indicates that CCL2 may contribute to periodontitis once its levels are directly correlated with gingival inflammation. It has been demonstrated that IL-1β and TNF-α induce and synergistically stimulate CCL2 expression by fibroblasts from human periodontal ligament contributing to the infiltration of monocytes into inflammatory sites (Hanazawa et al., 1993, Ozaki et al., 1996, Yu et al., 1995). The monocytes/macrophages accumulation at sites of bone injury and bone remodeling may play a significant role in the regulation of bone metabolism (Rahimi et al., 1995, Williams et al., 1992, Yada et al., 2010). CCL2 also has been implicated as chemoattractant for osteoclast precursors (Bonecchi et al., 2009, Garlet et al., 2003) while limiting the infiltration of PMNs (Garlet et al., 2010). Accordingly, it was demonstrated that the mean concentration of CCL2 in GCF in chronic periodontitis patients reduced after treatment (Pradeep et al., 2009). Thus, a variety of evidence that support the role of CCL2 in inflammatory bone remodeling conditions, such as PD and PL, include: 1) CCL2 is the principal monocyte chemoattractant produced by osteoblastic cells *in vitro*, 2) CCL2 is not expressed in normal bone, but is induced during bone inflammation, 3) The induction of CCL2 in inflamed bone is temporally and spatially correlated with the recruitment of monocytes, 4) CCL2 production is associated with the recruitment of monocytes to areas of both bone formation and resorption during developmentally regulated bone remodeling (reviewed by Yada et al., 2010).

Altogether, these findings indicate that chemokines orchestrate a large proportion of the cellular and molecular events observed in inflammatory oral diseases. In PD and PL, chemokines are directly involved in the recruitment of cells to control infection, but also contribute to the pathways involved in bone resorption. Thus, the control of this highly tuned system is essential in the determination of tissue homeostasis or disease when an infectious challenge disturbs the natural host balance.

7. Clinical implications and future directions

Periodontal disease and periapical lesion progression remain significant aspects of dentistry today. Extensive efforts to understand the etiology and pathogenesis of the oral inflammatory diseases concluded that they share common pathogenic mechanisms. Both diseases are mainly mediated by the perpetuation of infection and destruction of connective and mineralized tissues. This information gives us a clue that certain therapeutic strategies may be beneficial to both diseases and a number of mediators may have therapeutical potential. Ironically, the same host systems that defend against diverse pathogens are also responsible for tissue destruction. Hence, the spatial orientation of the inflammatory infiltrate to the bone and the periodontal tissue is an important component that can determine whether the destructive influence is predominant over the infection control. Despite recent technological advances in curative treatment, the disease prevention are still elusive. Deeper knowledge of the etiology and pathogenesis to uncover predictive biomarkers may well be important to provide safe host-modulating approaches, which can reveal real possibility of early intervention and prevention of alveolar bone loss.

8. Concluding remarks (Summary)

The past 20 years have seen major advances in our understanding of the role of cytokine networks and chemokines orchestrating cellular and molecular events in the complex process of inflammatory disease development and progression. In fact, the development of oral inflammatory diseases is characterized by the persistent release of inflammatory mediators, such as cytokines and chemokines and migration of inflammatory cells to infected sites. These responses, although directed against bacteria, perpetuate and mediate the destruction of connective and mineralized periodontal tissues, being the main responsible for periodontal breakdown. Moreover, ongoing research results let us to conclude that the discovery of new T cell subsets lead to a more complex scenario regarding the role of cytokines in inflammatory oral diseases pathogenesis. Recent reports suggest that the control of periodontal and periapical infection by "protective and destructive" mediators is an obviously simplified concept and several cytokines may present dual and apparently conflicting protective and destructive roles. Thus, string theories to unravel the destructive and protective role of cytokines and chemokines from the tissue destruction viewpoint make the development of effective therapies a very interesting challenge.

9. References

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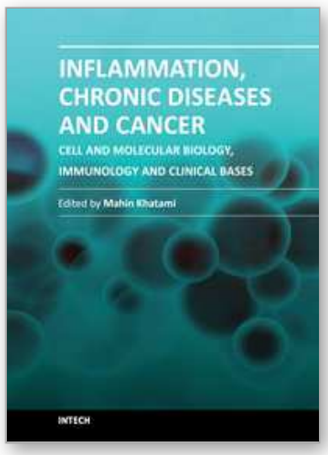

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This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The goal has been to demonstrate that persistent or chronic (unresolved or subclinical) inflammation is a common denominator in the genesis, progression and manifestation of many illnesses and/or cancers, particularly during the aging process. Understanding the fundamental basis of shared and interrelated immunological features of unresolved inflammation in initiation and progression of chronic diseases or cancer are expected to hold real promises when the designs of cost-effective strategies are considered for diagnosis, prevention or treatment of a number of age-associated illnesses such as autoimmune and neurodegenerative diseases as well as many cancers.

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