Inflammatory mediators in the pathogenesis of periodontitis

Tülay Yucel-Lindberg* and Tove Båge

Periodontitis is a chronic inflammatory condition of the periodontium involving interactions between bacterial products, numerous cell populations and inflammatory mediators. It is generally accepted that periodontitis is initiated by complex and diverse microbial biofilms which form on the teeth, i.e. dental plaque. Substances released from this biofilm such as lipopolysaccharides, antigens and other virulence factors, gain access to the gingival tissue and initiate an inflammatory and immune response, leading to the activation of host defence cells. As a result of cellular activation, inflammatory mediators, including cytokines, chemokines, arachidonic acid metabolites and proteolytic enzymes collectively contribute to tissue destruction and bone resorption. This review summarises recent studies on the pathogenesis of periodontitis, with the main focus on inflammatory mediators and their role in periodontal disease.

The inflammatory response is vital for our survival and occurs throughout many processes in our bodies. Among other things, inflammation is a necessary component for our defence against pathogens and in wound healing. In response to an injury or infection, acute inflammation occurs immediately and is usually short-lived. However, when inflammation remains unresolved, it evolves into chronic inflammation because host immune and inflammatory responses are insufficient to remove or clear the microbial challenge which initiates and perpetuates the disease. In chronic inflammation, tissue destruction and healing usually occur at the same time, but the balance is delicate and can tilt towards destruction. In the oral cavity, bacteria are constantly present and can trigger an inflammatory response to induce gingivitis, a reversible periodontal disease affecting gingival tissue. The balance between the resident microbiota and the host might be disrupted by either compromised host responses (e.g. poorly controlled diabetes mellitus) or an increase in the microbial challenge (e.g. cessation of oral hygiene procedures). In disease-susceptible individuals, gingivitis may progress into periodontitis, the irreversible stage of periodontal disease, with the presence of both gingival inflammation and clinical attachment loss.

Periodontal disease is common and around 5–15% of the population suffers from severe periodontitis (Refs 1, 2, 3, 4). The definition of periodontitis is based on a number of clinical criteria, including bleeding on probing, periodontal pocket depth and clinical attachment loss (Ref. 5). The specific use of these criteria however, varies substantially between different studies and cohorts, indicating a lack of consensus in the epidemiologic case definition of periodontitis and in measurement

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methods for the disease (Refs 5, 6). The primary hallmark of periodontitis, the destruction of periodontal tissue, is widely accepted to be a result of the host immune inflammatory response caused by periodontal microorganisms (Refs 7, 8).

The host response has traditionally been considered to be mediated mainly by B and T lymphocytes, neutrophils and monocytes/macrophages. These are triggered to produce inflammatory mediators, including cytokines, chemokines, arachidonic acid metabolites and proteolytic enzymes, which collectively contribute to tissue degradation and bone resorption by activation of several distinct host degradative pathways (Refs 9, 10). In recent years, resident cells in gingival connective tissue have also been revealed as important contributors to the inflammatory response and the increased levels of various inflammatory mediators (Refs 11, 12, 13). The role of the host response in periodontal disease is complex, and with regard to cell infiltration, polymorphonuclear leukocytes (PMNs), which are first to arrive, are the dominant cell type within the junctional epithelium and gingival crevice. Regarding inflammatory mediators, studies have previously demonstrated that cytokines, chemokines and prostaglandins, which are all within the scope of this review, play a critical role in periodontal tissue breakdown (Refs 14, 15, 16, 17). One important effector mechanism of the inflammatory mediators present in periodontal tissue is stimulation of the formation of osteoclasts, multinucleated cells believed to be the major cell type responsible for bone resorption (Refs 18, 19).

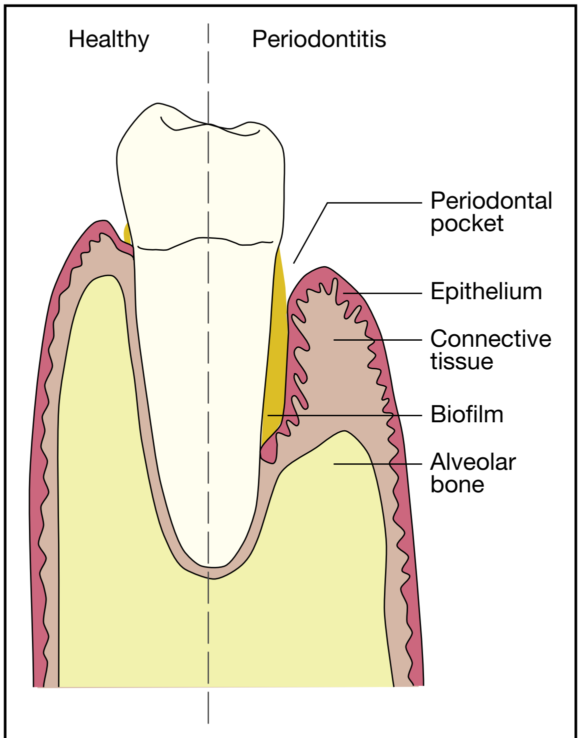

Figure 1. Characteristics of periodontitis. Healthy periodontal tissue (left) and periodontitis (right). Periodontitis is characterised by degradation of the soft connective tissue and alveolar bone supporting the tooth, ultimately resulting in tooth loss.

Pathogenesis of periodontitis

Besides dental caries, periodontal disease is one of the most prevalent diseases in the world and includes the major conditions gingivitis and periodontitis. The milder, reversible form of the disease, gingivitis, comprises inflammation of the gingival tissue. In disease-susceptible individuals, gingivitis may progress to periodontitis, which is a chronic inflammatory state of the gingiva causing destruction of connective tissue as well as of alveolar bone resulting in reduced support for the teeth and ultimately tooth loss (Fig. 1) (Refs 20, 21, 22).

The pathogenesis of periodontitis has been gradually elucidated during the later half of the 20th century. In the 1960s and 1970s, research on humans and animals showed that bacteria play a critical role in initiating gingivitis and periodontitis (Refs 23, 24, 25). Leading up to the 1980s, there were further advances within the field and the pivotal role of the host inflammatory response in disease progression began to emerge (Refs 26, 27, 28). The importance of hereditary factors was subsequently demonstrated in several studies, including those comparing monozygotic and dizygotic twins (Refs 29, 30). Systemic conditions and environmental factors such as smoking were also shown to greatly affect the disease onset and progress (Refs 7, 31, 32). For over a decade now, the concept of periodontitis has been considered to be a complex interaction between the microbial challenge and the host response, which alters connective tissue and

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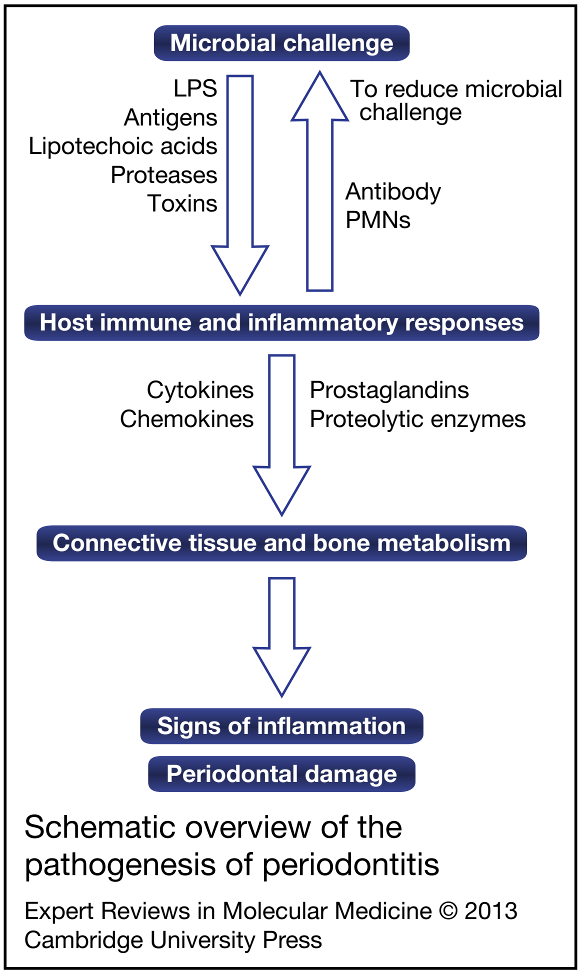

Figure 2. Schematic overview of the pathogenesis of periodontitis. The pathogenesis of periodontitis comprises of a complex interaction between the microbial challenge and the host response, resulting in an altered bone metabolism. Bacterial components of the biofilm, such as LPS, antigens and toxins initiate a host immune and inflammatory response which activates host defence cells including PMNs and triggers an antibody response directed towards reducing the magnitude of the microbial challenge. Activation of defence cells results in the production of inflammatory mediators such as cytokines, chemokines, prostaglandins and proteolytic enzymes (e.g. MMPs) that alter connective tissue and bone metabolism. If host immune and inflammatory responses are insufficient to remove or clear the microbial challenge, a chronic inflammatory response develops leading to periodontal inflammation (redness, swelling and bleeding) and periodontal damage (clinical attachment loss). LPS, Lipopolysaccharide; MMPs, matrix metalloproteinases; and PMNs, polymorphonuclear leukocytes.

bone metabolism and causes periodontal damage, i.e. clinical attachment loss (Fig. 2) (Ref. 7). Each of these parts is complex in its own right, but the focus of this review will be on the host response and the intricate network of inflammatory mediators that orchestrate it.

Host response

Bacterial components, such as lipopolysaccharides (LPS), peptidoglycans, lipoteichoic acids, proteases and toxins, which instigate the inflammatory reaction, can be found in the biofilm on tooth surfaces (Refs 31, 32). The host response to the bacterial challenge includes the action and stimulation of various inflammatory cell types as well as of resident cells of the tissue, as schematically illustrated in (Fig. 3) (Refs 7, 33, 34, 35, 36, 37). The "red complex" comprising the pathogens *Tannerella forsythia*, *Porphyromonas gingivalis* and *Treponema denticola*, has been demonstrated in the biofilms at sites expressing progressing periodontitis (Refs 38, 39). Antigens and products, such as LPS and peptidoglycans, released by bacteria are recognised by toll-like receptors (TLRs) on the surface of host cells, which initiates an inflammatory response (Ref. 40).

Through a cascade of events, mast cells are stimulated to release vasoactive amines and preformed tumour necrosis factor α (TNFα), which increases vascular permeability and the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and P-selectin on endothelial cell surfaces (Refs 32, 34). This process recruits PMNs into the tissue, where they release lysosomal enzymes, which contribute to tissue degradation (Ref. 34). In response, lymphocytes and macrophages further invade the tissue. At this point, 60−70% of the collagen in the gingival connective tissue is degraded at the site of the lesion, but the bone is still intact (Refs 26, 34). At this stage, it is still possible for gingival tissues to repair and remodel without permanent damage. However, in some individuals, owing to innate susceptibility and/or environmental factors, the inflammation fails to resolve, with subsequent connective tissue breakdown and irreversible bone loss (Refs 34, 41, 42). In this scenario, macrophages form pre-osteoclasts which, after maturing into osteoclasts, are capable of degrading alveolar bone (Ref. 18).

Without active resolution of inflammation, the bacterial antigens eventually encounter antigen-

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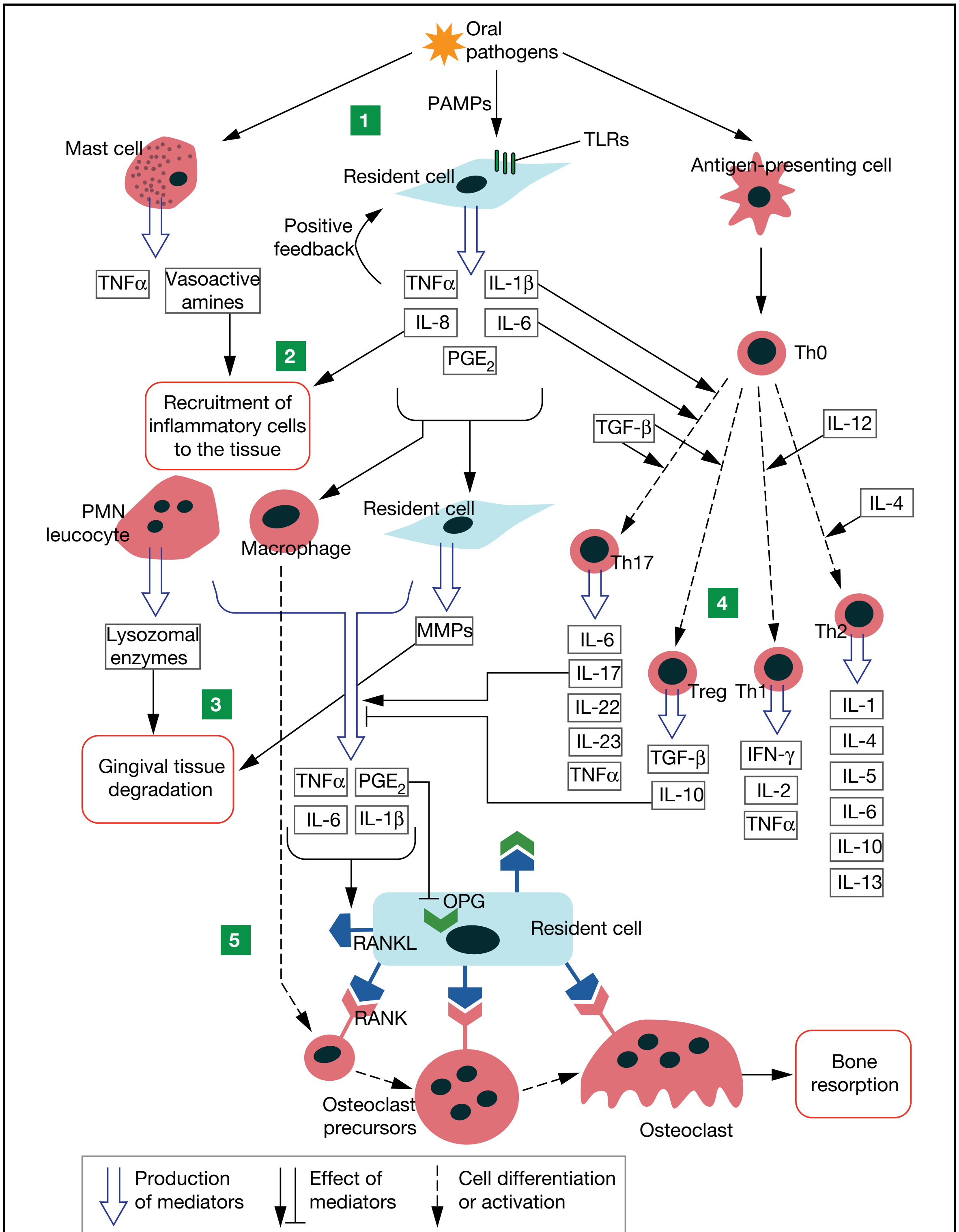

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Figure 3. Inflammatory mediators in the pathogenesis of periodontitis (*See next page for legend.*)

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presenting cells such as dendritic cells, macrophages and B cells. When naïve CD4 T helper cells (Th0) interact with antigen-presenting cells, naïve T cells differentiate into various subsets of cells including Th1, Th2, Th17 and regulatory T cells (Tregs), depending on the cytokines which they produce. Th1 cells drive the cell-mediated immune response and produce interferon-γ (IFN-γ), transforming growth factor-β (TGF-β), interleukin-2 (IL-2) and TNFα in the presence of IL-12. Th2 cells mediate the humoral immune response and produce the cytokines IL-4, IL-5, IL-6, L-10, IL-13 and TGF-β in the presence of IL-4. The additional two CD4 T cells, Th17 and Tregs play a critical role in autoimmunity and in the maintenance of immune homoeostasis. The TH17 subset of cells secrete IL-17, IL-23, IL-22, IL-6 and TNFα in the presence of TGF-β, IL-1β and IL-6 whereas Tregs arise in the presence of TGF-β and secrete the immunosuppressive cytokines IL-10 and TGF-β. Notably, IL-17 stimulates the production of various inflammatory mediators including TNFα, prostaglandin E_2 (PGE_2), IL-6 and IL-1β, mediating bone resorption via osteoclasts activation. Defective regulation of the immune system by Treg cells, thought to mediate the resolution of inflammation, contributes to the pathogenesis of several autoimmune diseases, such as rheumatoid arthritis (RA), multiple sclerosis and colitis (Refs 34, 35, 36, 37, 43, 44). Tregs and Th17 cells have been demonstrated to occur in periodontal tissue with an increased expression of Foxp3 and IL-17, characteristic markers of Tregs and Th17 cells, in periodontitis suggesting an important role for these cells in the immunoregulation of periodontitis (Refs 34, 37, 45). Numerous studies, however, indicate a plasticity between Treg and Th17 cell subsets which coexist in the same tissues, including periodontitis lesions (Ref. 45). Further studies are thus required to elucidate the role of the balance between the T cell subsets, Treg/Th17 and Th1/Th2, and their cross-talk in the pathogenesis of periodontitis.

Besides invading inflammatory cells, which produce inflammatory mediators and drive the inflammatory process, resident gingival cells may also affect the progression and persistence of periodontitis. Blood vessels, consisting of endothelial cells and smooth muscle cells, are the first to come in contact with invading inflammatory cells. In gingival connective tissue, the most ubiquitous resident cells are gingival fibroblasts. By producing inflammatory mediators, such as cytokines, chemokines, proteolytic enzymes and prostaglandins, these cells participate in the inflammatory response and contribute to disease persistence (Refs 31, 46, 47, 48, 49, 50, 51). Periodontal ligament fibroblasts, located between the tooth and the alveolar bone, are also involved in the inflammatory reaction and produce inflammatory mediators such as prostaglandins, proteolytic enzymes and factors which affect bone resorption (Refs 52, 53, 54). Throughout each step of the inflammatory process, proinflammatory mediators are released which affect various cell types and propel the inflammatory cascade. These mediators, which are the focus of this

Figure 3. Inflammatory mediators in the pathogenesis of periodontitis. (*Legend; see previous page for figure.*) The host response in periodontitis is a complex interplay between numerous cell types and inflammatory mediators, some of which are illustrated here. (1) In innate immunity, components of the pathogens present in the oral biofilm, such as LPS, stimulate mast cells to release vasoactive amines and preformed TNFα and cause a release of inflammatory mediators in resident cells of the gingival tissue. (2) Through the action of the released mediators, inflammatory cells are recruited into the tissue. (3) PMN leucocytes release lysosomal enzymes, and in response to the milieu of inflammatory mediators, MMP levels increase. MMPs and lysosomal enzymes contribute to degradation of the gingival tissue. (4) Lymphocytes and macrophages invade the tissue. Antigen-presenting cells activate Th0 cells. T-cell-produced cytokines can increase or inhibit the production of inflammatory mediators. (5) Cytokines and PGE_2 affect RANKL and OPG expression, resulting in the formation and activation of osteoclasts capable of alveolar bone degradation. IFN-γ, interferon-γ; IL, interleukin; LPS, Lipopolysaccharide; MMP, matrix metalloproteinase; OPG, osteoprotegerin; PAMPs, pathogen-associated molecular patterns; PGE_2, prostaglandin E_2; PMN, polymorphonuclear leukocytes; RANK, receptor activator of nuclear factor-κB; RANKL, receptor activator of nuclear factor-κB ligand; TGF-β, transforming growth factor β; TLRs, toll-like receptors; TNFα, tumour necrosis factor α; and Treg, regulatory T cell.

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review, include proinflammatory cytokines, chemokines and arachidonic acid metabolites such as prostaglandins.

Cytokines and chemokines

Numerous cytokines and chemokines have been detected in the gingival crevicular fluid (GCF), exudates collected at the gingival margin, and in gingival tissue from patients with periodontitis. Table 1 summarises the changes in cytokine and chemokine levels determined in GCF and gingival tissue during periodontitis and the effect of periodontal treatment on these levels.

Several proinflammatory cytokines including IL-1, IL-6, IL-12, IL-17, IL-18, IL-21, TNFα and IFN-γ have been demonstrated to be involved in the pathogenesis of periodontitis. The prominent cytokines IL-1 and IL-6, for example, are produced in the B-cell/plasma cell response which characterises the progression of periodontitis (Ref. 34). IL-6 is produced by epithelial cells, lymphocytes, monocytes and fibroblasts in response to bacterial LPS, IL-1 and TNFα and has been shown to stimulate the formation of osteoclasts in vitro (Refs 32, 84). Enhanced levels of IL-6 have been demonstrated in the GCF of patients with periodontitis, compared with healthy controls, and higher expression of IL-6 was reported in diseased gingival tissues when compared with healthy tissue in periodontitis patients (Refs 71, 85). Similarly, increased circulating systemic levels of IL-6 decreased after nonsurgical periodontal therapy resulting in clinical improvement of the periodontal status (Ref. 86).

The inflammatory cytokines IL-1 and TNFα play a prominent role in the pathogenesis of periodontitis (Ref. 87). As mentioned above, TNFα is involved at an early stage in the inflammatory cascade, as it is released from mast cells in response to bacterial challenge. In the clinical context, TNFα and IL-1β have been found in increased concentrations in GCF and gingival tissue of periodontitis sites (Refs 79, 88, 89), and levels are reported to decrease after treatment of periodontal disease (Refs 55, 59). The pivotal role of these cytokines in periodontitis is further supported by reports that attachment loss is reduced in periodontitis patients with RA after anti-TNF treatment and that the administration of recombinant TNFα or IL-1 to the gingiva exacerbates experimental periodontitis in rats (Refs 90, 91, 92). In addition, soluble receptors of IL-1 and TNF have been shown to greatly inhibit the progress of periodontitis in a primate model (Refs 14, 93). At the cellular level, these two cytokines are involved in the induction of several other inflammatory mediators, such as IL-6, IL-8, matrix metalloproteinases (MMPs) and PGE_2 (Refs 20, 32, 94, 95, 96). The cellular mechanisms underlying the direct involvement of TNFα and IL-1β in inducing bone resorption are covered later in this review. The cytokines TNFα and IL-1 are themselves synthesised by many cell types in the periodontal tissue: monocytes/macrophages, PMN cells, fibroblasts, epithelial cells, endothelial cells and osteoblasts (Ref. 87). These two cytokines seem to occupy a spider-in-the-web position among mediators of the inflammatory cascade in periodontitis. However, there is substantial interplay between numerous cytokines involved in the inflammatory response, and studies are ongoing to identify additional key players for future treatment and management of inflammatory diseases.

Chemokines are cytokines involved in inducing chemotaxis in responsive cells. In periodontitis, the chemokines IL-8, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP1α) attract neutrophils and other leucocytes to the inflammation site. IL-8 is secreted by various cells, including monocytes, lymphocytes, epithelial cells, endothelial cells and fibroblasts, in response to IL-1, TNFα and LPS (Refs 20, 97). High levels of IL-8 expression have been shown to be localised to sites with high concentrations of PMN cells in gingival tissue from patients with aggressive periodontitis (Ref. 98). In addition, enhanced levels of IL-8 were demonstrated in the GCF collected from periodontitis sites compared with healthy control sites and IL-8 levels decreased after periodontal therapy (Ref. 72). The chemokine MCP-1 is produced by endothelial cells, epithelial cells and fibroblasts in response to bacterial components such as LPS or inflammatory mediators (Refs 32, 99). The involvement of MCP-1, and also MIP1α and RANTES (regulated on activation, normal T cell expressed and secreted), in periodontitis is supported by studies demonstrating increased levels of the chemokines in gingival biopsies and/or GCF of patients with periodontitis, as well as decreased levels of chemokines in the

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Table 1. Cytokine levels in the gingival crevicular fluid and in gingival tissue

Cytokine	Role of cytokine	Change in periodontitis	Change after treatment
IL-1α	Proinflammatory	Increased in GCF (Refs 55, 56, 57), with correlation to clinical parameters (Ref. 58)	Decreased in GCF (Refs 55, 56)
IL-1β	Proinflammatory	Increased in GCF (Refs 55, 56, 57, 59, 60, 61), with correlation to clinical parameters (Refs 58, 62, 63, 64) Increased protein expression (Refs 65, 66)	Decreased total amount (Refs 55, 56, 59) Increased concentration in GCF (Ref. 67)
IL-4	Anti-inflammatory	Decreased total amount in GCF (Ref. 60) Increased total amount in GCF (Refs 57, 64) Decreased concentration in GCF (Ref. 64) Increased concentration in GCF (Ref. 68)	Increased in GCF (Refs 68, 69, 70)
IL-6	Proinflammatory	Increased in GCF (Refs 57, 61, 71) with correlation to clinical parameters (Ref. 63)	Decreased in GCF (Ref. 56)
IL-8	Chemokine	Increased in GCF (Refs 57, 59, 61) with correlation to clinical parameters (62, 63)	Decreased in GCF (Refs 56, 59, 72)
IL-10	Anti-inflammatory	Increased total amount in GCF (Refs 59, 64), correlated to clinical parameters (Ref. 63) Increased concentration in GCF (Ref. 59) Decreased concentration in GCF (Ref. 64)	Decreased in GCF (Ref. 59)
IL-12 (p40)	Proinflammatory	Increased in GCF (Ref. 57) Increased protein expression (Ref. 73)	Decreased in GCF (Ref. 56)
IL-17	Proinflammatory	Increased mRNA expression (Ref. 74) Increased in GCF (Ref. 75)	Decreased in GCF (Refs 70, 75)
IL-18	Proinflammatory	Increased in GCF with correlation to clinical parameters (Ref. 76)	Decreased in GCF (Ref. 76)
IL-21	Proinflammatory	Increased in GCF (Ref. 77)	Decreased in GCF (Ref. 70)
IFN-γ	Proinflammatory	Increased in GCF (Refs 57, 78) Increased mRNA expression (Ref. 78)	Decreased in GCF (Refs 56, 69) No changes in GCF (Ref. 70)
TNFα	Proinflammatory	Increased in GCF with correlation to clinical parameters (Refs 62, 63, 79) Increased protein expression (Ref. 80)	Increased concentration in GCF (Ref. 67) No change in GCF (Ref. 81) Decreased in GCF (Ref. 82)

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Table 1. Cytokine levels in the gingival crevicular fluid and in gingival tissue *(continued)*

Cytokine	Role of cytokine	Change in periodontitis	Change after treatment
MCP-1	Chemokine	Increased in GCF (Ref. 57) with correlation to clinical parameters (Refs 76, 79) Increased mRNA expression (Ref. 83)	Decreased in GCF (Refs 56, 76)
MIP1α	Chemokine	Increased in GCF (Ref. 57)	Decreased in GCF (Ref. 56)
RANTES	Chemokine	Increased in GCF (Refs 57, 59) Increased mRNA expression (Ref. 83)	Decreased in GCF (Refs 56, 59)

GCF volumes increase with increasing size of periodontal pockets, which is a hallmark of periodontitis. Owing to the large variations between healthy and diseased GCF volumes, changes in total amount and concentration of the inflammatory mediators may differ. Whether the data are a total amount or a concentration is noted in relevant cases
GCF, gingival crevicular fluid; IL, interlukin; IFN-γ, interferon-γ; TNFα, tumour necrosis factor α; MCP-1, monocyte chemoattractant protein-1; MIP1α, macrophage inflammatory protein-1α; RANTES, regulated on activation, normal T cell expressed and secreted.

GCF after periodontal treatment (Refs 56, 57, 59, 76, 79, 83).

Various cytokine gene polymorphisms have been reported to be associated with periodontitis (Refs 100, 101). Gene polymorphisms in the genes for IL-1, TNF*α*, IL-6 and IL-10 as well as combined genotypes of TNF*α* and lymphotoxin alpha have been reported in patients with periodontitis (Refs 102, 103, 104, 105, 106). These reports support the view of periodontitis as a disease that is largely dependent on the manner of the inflammatory response to components of the oral biofilm. The nature of the inflammatory response is collectively influenced by individual genetic differences in the host, specific components of the oral microbiome and past history of periodontal infection.

Arachidonic acid metabolites – prostaglandins

A range of arachidonic acid metabolites are produced in the gingival tissues. These eicosanoids include prostanoids and leukotrienes, which are produced from arachidonic acid through distinct enzymatic systems. Leukotrienes, known to play an important role in asthma and allergy, are also involved in bone remodelling (Refs 107, 108). Their involvement in periodontitis remains to be investigated, although some data indicate raised levels of the mediators in the disease (Refs 109, 110). Leukotriene B_4 (LTB_4) in particular has been implicated in RA, which is highly similar to periodontitis in that it is a chronic inflammatory condition which affects bone remodelling. A possible role for LTB_4 has been suggested in the progression of periodontal disease because of the findings that the substantial increase in GCF LTB_4 concentrations, which are associated with the severity of periodontal disease, decreased following periodontal treatment (Ref. 109). Some leukotrienes also have anti-inflammatory effects, and one such leucotriene investigated in relation to periodontal disease is Resolvin E_1 (RvE_1). This anti-inflammatory eicosanoid has been reported to down-regulate inflammation-induced bone loss in experimental periodontitis (Ref. 111) and inhibit osteoclast growth and bone resorption by interfering with osteoclast differentiation (Ref. 112). It was also recently reported that RvE_1 restored impaired phagocytic activity in macrophages from the blood of patients with aggressive periodontitis (Ref. 113) and inhibited LTB_4-induced production of the antimicrobial peptide LL-37 from PMNs, thus terminating the LL-37/LTB_4 proinflammatory circuit (Ref. 114).

Prostaglandins are a group of potent arachidonic acid-derived inflammatory mediators with the capacity to induce a wide variety of biological responses (Ref. 115). They influence many biological processes, including vasodilatation, vascular permeability, oedema, pain and fever, and the mediator also play an immunoregulatory role in neutrophil and

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monocyte chemotaxis (Ref. 116). Prostaglandins, synthesised by virtually all mammalian cells, are local hormones, acting at or near the site of their synthesis. They function in both an autocrine and a paracrine fashion and modulate the responses of other hormones, which have profound effects on many cellular processes (Refs 115, 117, 118, 119). Among prostaglandins, PGE_2 is the most prominent in the pathogenesis of periodontitis (Refs 108, 120). PGE_2 is produced by immune cells, fibroblasts and other resident gingival cells and has a wide range of biological effects on the cells of the diseased gingiva (Refs 46, 120). The actions of PGE_2 include the stimulation of inflammatory mediators and MMPs, as well as osteoclast formation via receptor activator of nuclear factor-κB ligand (RANKL) (Refs 120, 121, 122). The effect of PGE_2 on a specific cell type depends on the prostaglandin receptors, EP_1 through EP_4. The receptors most relevant to the pathogenesis of periodontitis are EP_2 and EP_4, which are reported to activate adenylate cyclase and protein kinase A signalling (Ref. 123). In rodent models, these two receptors have been shown to be involved in bone resorption in response to PGE_2 (Refs 124, 125).

Several clinical alterations observed in periodontal disease can be associated with PGE_2, especially when IL-1 and TNFα are present in the gingival tissue. PGE_2 is detected at significantly higher levels in human inflamed gingival tissue and especially from periodontal sites exhibiting recent attachment loss (Refs 126, 127, 128). Higher levels of PGE_2 are also found in the GCF of patients with periodontitis compared with levels found in GCF of healthy individuals (Refs 129, 130, 131). Accordingly, increasing levels of PGE_2 in crevicular fluid have been suggested to serve as a predictor of periodontal attachment loss (Ref. 132). Furthermore, polymorphisms within the cyclooxygenase-2 (COX-2) gene as well as the methylation levels within the COX-2 promoter, which affect COX-2 mRNA expression, have been repeatedly implicated in periodontitis (Refs 133, 134). Altogether, over-production of PGE_2 is suggested to have a significant role in the pathobiology of periodontitis (Refs 127, 129, 135).

Inflammatory mediators and tissue destruction

Maintenance of the extracellular matrix is important for normal development and function of gingival tissue. Proteolytic MMP enzymes and their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs), are involved in the homoeostasis of the extracellular matrix in healthy tissue, but they are also key players in the process of tissue destruction in inflammatory diseases. Besides modifying the extracellular matrix, MMPs are also involved in regulating the activities of cytokines and cytokine receptors. In periodontitis, both host- and bacteria-derived proteolytic enzymes contribute to the degradation of the extracellular matrix of the connective tissue. Numerous host proteolytic enzymes such as MMPs, elastase, mast cell tryptase, dipeptidyl-peptidase, plasminogen activators and the lysosomal cysteine proteinases, cathepsins and protease 3 have been detected in the GCF of patients with periodontitis (Refs 136, 137). Increased expressions of MMPs (gelatinase and collagenase) are associated with pathological conditions including RA and periodontitis.

MMP expression and activity are in general low in noninflamed periodontium but increase to pathologically high levels in inflamed gingiva, where increased levels of inflammatory mediators upregulate MMP expression (Ref. 138). Studies also suggest, however, that MMP-8 and -9 have the capacity to exert anti-inflammatory effects by processing anti-inflammatory cytokines and chemokines (Refs 138, 139, 140, 141). Among the MMPs, levels of MMP-8 and -13 have been correlated with the severity of periodontal disease (Refs 10, 138, 142). In addition, MMP-8, TIMP-1 and carboxyterminal telopeptide of type I collagen (ICTP) and especially their ratios and combinations are potential candidates in the detection of advanced periodontitis through salivary diagnostics (Ref. 143). Recently, it was reported that MMP-3 and TIMP-1 mRNA expression were significantly higher in diseased tissues than control tissues and that polymorphisms of MMP-3 and TIMP-1 are associated with chronic periodontitis (Ref. 144). In addition, MMP-1, MMP-3 and MMP-9 polymorphisms were newly demonstrated to be associated with susceptibility to periodontitis in a Chinese population (Ref. 145).

In in vitro studies, the inflammatory mediators IL-1β, TNFα and bacterial LPS upregulate MMP-1, -3, -8 and -9 expression in gingival fibroblasts (Refs 146, 147, 148, 149). Moreover, the periodontal pathogen *Porphyromonas gingivalis*, in

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the presence of cigarette smoke condensate, increases collagen degradation and protein levels of MMP-1, -2, -3 and -14 in gingival fibroblasts (Ref. 150). The cytokine IL-1β stimulates MMP-2 expression via a PGE_2-dependent mechanism in human chondrocytes (Ref. 151). The close interactions between PGE_2 and the MMPs are further emphasised by the key role of PGE_2 in the regulation of MMP-9 expression in macrophages and in the induction of MMP-3 and MMP-13 in chondrocytes via the PGE_2-regulatory enzyme microsomal prostaglandin E synthase-1 (mPGES-1) (Refs 152, 153). Moreover, PGE_2 stimulates MMP-1 production in human gingival fibroblasts via activation of mitogen-activated protein kinases (MAPKs)/activator protein-1 (AP-1) and nuclear factor-κB (NF-κB) (Ref. 154) and in mouse osteoblasts via the cAMP-PKA signalling pathway (Ref. 155).

The TIMPs that control MMP activity and thereby act as regulators of MMP-mediated extracellular matrix breakdown play an important role in tissue remodelling and the pathology of periodontal tissue destruction (Ref. 156). TIMP levels are generally higher in healthy periodontal tissue compared with inflamed periodontal tissue, resulting in an excess of MMP levels over TIMP-1 levels (Ref. 156). In GCF samples, levels of TIMP-1 and -2 are decreased whereas the levels of MMP-1, -2, -3 and -9 are increased in periodontitis-affected patients compared with healthy controls (Ref. 157). MMP inhibition via nonantimicrobial tetracyclines such as doxycycline has been suggested as a potential treatment of chronic inflammatory diseases, including periodontitis. It has been shown that treatment with doxycycline, as an adjunct to periodontal treatment, suppressed collagenase activity in the periodontal pocket of patients with periodontitis (Ref. 158), which suggests significant therapeutic potential for nonantimicrobial tetracyclines in treatment of periodontal disease.

Inflammatory mediators and bone resorption

Bone resorption is a well-regulated process which depends on the differentiation of monocytes to osteoclasts capable of bone resorption. Although bone formation and bone resorption are processes which occur continuously in healthy alveolar bone, in periodontitis, the normal balance is shifted towards resorption through mechanisms including increased osteoclast activation. Cytokines such as IL-1β, TNFα, IL-6, macrophage colony-stimulating factor (M-CSF), IL-17 and PGE_2 are among the more important proinflammatory mediators reported to stimulate osteoclast activation (Refs 159, 160). The TNF family cytokine RANKL induces the differentiation of osteoclasts in the presence of M-CSF (Ref. 161) and activates TRAF6 (member of TNF receptor associated factor), c-Fos and calcium signalling pathways, which are indispensable for the induction and activation of nuclear factor of activated T cells (NFAT) c1, a key transcription factor for osteoclastogenesis. Recently, it was also demonstrated that Wnt5a, a member of the highly conserved Wnt protein family, upregulates RANK expression in osteoclast precursors enhancing RANKL-induced osteoclastogenesis proposing Wnt5a as a new co-stimulatory cytokine for osteoclastogenesis (Ref. 162). In the context of periodontitis, elevated levels of RANKL and reduced levels of osteoprotegerin (OPG) were detected in the GCF samples of patients with periodontitis and the RANKL/OPG ratio was suggested as a possible biomarker test for detection of bone destruction (Ref. 163). OPG acts as a decoy receptor for RANKL and inhibiting OPG expression enables RANKL to interact with its receptor RANK on other cells. RANKL then binds to RANK on osteoclast lineage cells to drive differentiation to osteoclasts (Fig. 3) (Refs 18, 123). The ratio of the GCF levels of RANKL and OPG was higher in patients with periodontitis compared with healthy subjects, suggesting that increased RANKL and/or decreased OPG contribute to osteoclastic bone destruction in periodontal disease (Ref. 164).

IL-1 and TNF stimulate bone resorption by increasing osteoclast formation (Ref. 165) and furthermore, IL-1 also mediates the osteoclastogenic effect of TNF by enhancing expression of RANKL and differentiation of osteoclast precursors (Ref. 166). Inflammatory cytokines such as IL-1β induce RANKL and/or OPG expression in several cell types, including osteoblasts, gingival fibroblasts and periodontal ligament fibroblasts (Refs 54, 167). Similarly, IL-6, produced and secreted by various cells including fibroblasts and osteoblasts, induces osteoclast formation and stimulates bone resorption and IL-6 receptor blockade/antagonist strongly reduces osteoclast formation in inflamed joints and bone erosion in vivo

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(Ref. 168). The importance of RANKL and its downstream transcription factor NF-κB in inflammation-induced bone resorption has been shown in collagen-induced arthritis in mice, where blocking of NF-κB reduced disease severity by decreasing TNFα and IL-1β levels, abrogating joint swelling and reducing destruction of bone and cartilage (Ref. 169).

The major pathway by which the inflammatory mediator PGE_2 stimulates bone resorption is generally considered to be via the up-regulation of RANKL expression and the inhibition of OPG expression in osteoblastic cells (Ref. 123). In osteoclastogenesis, the stimulatory effect of oral pathogen sonicates has been demonstrated to be mainly mediated through the PGE_2/RANKL pathway in primary mouse osteoblasts co-cultured with bone marrow cells (Ref. 170). It has also been reported that RANKL-stimulated osteoclastogenesis can be enhanced by PGE_2 and LPS through direct effects on the haematopoietic cell lineage (Ref. 121). PGE_2 has been shown both to inhibit and stimulate OPG expression (Refs 54, 171), a contradiction which may be the result of differing incubation times, as has been suggested for the effect of PGE_2 on osteoclast formation (Ref. 123).

Modulation of host response

Periodontitis is a complex disease in which the host immune inflammatory response caused by the bacterial challenge results in connective tissue destruction and bone resorption. During disease activity, numerous inflammatory cells and resident cells in the periodontium express and/or stimulate inflammatory mediators including PGE_2, cytokines, chemokines, MMPs and proteins of signal transduction pathways collectively contributing to the destruction of soft and hard tissue. Traditional periodontal therapy has focused on decreasing the microbial challenge by mechanically disrupting and removing bacterial biofilms that form on tooth surfaces and adjacent soft tissue. A growing number of studies, however, have indicated strong potential for adjunctive host-modulating drugs as new therapeutic strategies in the management of periodontal disease (Refs 172, 173).

Inhibition of inflammatory mediator PGE_2

The biosynthesis of PGE_2 involves three different groups of enzymes acting sequentially. The first group of enzymes, phospholipase A_2 (PLA_2), converts membrane lipids to AA (Refs 174, 175). The second group of isoenzymes, COX-1 and COX-2, convert AA to prostaglandin H_2 (PGH_2) (Ref. 176). Multiple enzymes then metabolise the intermediate PGH_2 to diverse prostaglandins, including PGE_2, PGF_2, PGD_2 and PGI_2 (Refs 176, 177). The third group of isoenzymes, prostaglandin E synthase (PGE synthase), which is the terminal enzyme in the synthesis of PGE_2, catalyses the conversion of COX-derived PGH_2 to PGE_2 (Refs 178, 179).

As Nobel Laureate John R. Vane first suggested in 1971 (Ref. 180), the COX enzymes are the primary targets for nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin. NSAIDs inhibit the first step of the reaction, the formation of PGG_2. Specific COX-2 inhibitors have been developed to achieve inhibition of inflammation-induced PGE_2 production without the detrimental inhibition of baseline, COX-1-derived prostaglandin production was thought to account for the gastrointestinal side-effects of traditional NSAIDs (Ref. 181). Treatment strategies with nonselective NSAIDs and selective COX-2 inhibitors have suggested a potential adjuvant role for COX-inhibitors in periodontal therapy (Ref. 182). Evidence from animal experiments and clinical trials demonstrates that both NSAIDs and selective COX-2 inhibitors are generally responsible for stabilisation of periodontal conditions by reducing the rate of alveolar bone resorption (Ref. 183). Recently, it was also reported, in a small sample size, that "low-dose" aspirin may reduce the risk of periodontal attachment loss (Ref. 184). In contrast, adjunctive treatment with oral administration of meloxicam does not seem to improve clinical parameters or GCF levels of PGE_2 and IL-1β (Ref. 185). In experimental periodontitis of rats, the selective COX-2 inhibitor celecoxib and prophylactic omega-3 fatty acid, alone and in combination, inhibit gingival tissue MMP-8 expression (Ref. 186).

However, COX-2-specific drugs have several side-effects, including cardiovascular problems (Ref. 187), and one of the COX-2-specific pharmaceutical inhibitors, Vioxx, was withdrawn from the market because of these side-effects. Owing to the side-effects experienced during COX enzyme inhibition, particular attention has been given to the downstream enzymes of the PGE_2 cascade synthesis. Recently, several

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different groups of compounds that inhibit mPGES-1 activity have been described (Refs 188, 189). One of the most promising groups of inhibitors are the disubstituted phenanthrene imidazoles, which were found to be orally active in a guinea pig model (Ref. 190). The indole 5-lipoxygenase-activating protein inhibitor MK-886 and its derivatives have been shown to inhibit mPGES-1 in enzyme assays (Ref. 191). Furthermore, natural products such as curcumin (Ref. 192) (from the spice turmeric) and epigallocatechin-3-gallate (Ref. 193) (from green tea) have been shown to affect mPGES-1 in vitro. Several mPGES-1 inhibitors are being studied in animal models, but none are as yet available for use in humans (Refs 194, 195, 196, 197). In experimental periodontitis in rats, the mPGES-1 inhibitor curcumin effectively inhibited cytokine gene expression at the mRNA and the protein level and inhibited activation of NF-κB in the gingival tissues although the inhibitor did not prevent alveolar bone resorption (Ref. 198). It was also recently reported that aminothiazoles targeting mPGES-1 decrease PGE_2 synthesis in vitro and ameliorate experimental periodontitis in vivo (Ref. 199). PGE_2 inhibitors, targeting the enzyme COX using NSAIDs or specific COX-2 inhibitors, have been shown to block periodontal PGE_2 synthesis and prevent disease progression in numerous animal models and a few clinical studies (Refs 183, 200). Well-designed, large-scale clinical trials are needed to further evaluate the role of PGE_2 inhibitory drugs as new therapeutic strategies in the management of periodontal disease.

Inhibition of proinflammatory cytokines

Cytokines have been validated as therapeutic targets for treatment of numerous inflammatory diseases such as RA, inflammatory bowel disease (IBD) and periodontitis. TNFα was the first cytokine to be validated as a therapeutic target for RA, and although several other cytokine antagonists including TNFα, IL-1 and IL-6 have been or are being validated as biological therapies for treatment of RA, TNFα seems to be the preferred target of first-line biological therapy (Ref. 201). Soluble antagonists to IL-1 and TNFα, at this time only demonstrated in experimental periodontitis, have shown a reduction in loss of connective tissue attachment, osteoclast formation and loss of alveolar bone (Refs 15, 87, 93). However, although a few studies have reported a reduction of alveolar bone loss in patients with RA in response to anti-TNFα treatment, there are limited results suggesting that anti-TNFα agents can reduce local production of inflammatory cytokines and periodontal inflammation in RA patients with periodontitis (Ref. 202).

Levels of inflammatory cytokines and other mediators can also be regulated through inhibition of intracellular signalling pathways. Induction of cytokines in response to activation of TLRs by bacterial pathogens involves numerous signal transduction pathways including NF-κB, MAPK and janus kinase-signal transducer and activator of transcription (JAK-STAT). The MAPK signal pathway comprises of the subfamilies extracellular regulated kinases (ERKs) and the c-Jun N-terminal activated kinases (JNK) and p38. Inhibitors that target JNK have been suggested to have therapeutic potential in the chronic inflammatory conditions RA and IBD (Refs 203, 204). Recently, it was reported that silencing the MAP kinase-activated protein kinase-2 (MAPKAPK-2) impeded LPS-induced inflammatory bone loss, decreased the inflammatory infiltrate and reduced osteoclastogenesis (Ref. 205). Moreover, studies on experimental rat periodontitis suggest that orally active p38 MAPK inhibitors can reduce LPS-induced inflammatory cytokine production and osteoclast formation and protect against LPS-stimulated alveolar bone loss and decreased IL-6, IL-1β and TNFα expression (Ref. 206). This highlights the importance of p38 MAPK signalling in immune cytokine production and periodontal disease progression (Ref. 207).

Cytokine expression is also endogenously regulated through post-transcriptional modulations that affect mRNA stability, known to play an important role in inflammatory disease progression. Cytokines such as TNFα, IL-6 and IL-8, which activate multiple signalling cascades including ERK, JNK, NF-κB and p38 MAPK are regulated via mRNA stability. The absence of post-transcriptional regulation of the mRNAs of these cytokines may increase cytokine production, leading to tissue destruction (Ref. 208). Thus, RNA-binding proteins and microRNAs, which bind to the AU-rich elements of cytokine mRNA that affect mRNA stability, have been suggested as

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potential new treatments for controlling the cytokine mRNA expression (Ref. 208).

Research in progress and conclusions

Continuing advancement in scientific methodology, including high throughput analysis techniques, is enabling studies on genomic variations and gene expression patterns in periodontal disease. Whole-genome microarrays and RNA sequencing will be valuable tools for identifying genetic and biological markers of increased susceptibility to periodontal disease. In recent years, both transcriptome studies and a genome-wide association study have been performed on periodontitis cohorts (Refs 209, 210, 211, 212). The massive amounts of data generated by such studies require painstaking analyses to yield biologically significant results, but the capacity for identification of novel mediators involved in the pathogenesis of periodontitis is promising, especially in sequencing approaches that are unhampered by predefined probe sets (Refs 213, 214). However, upcoming breakthroughs in the understanding and treatment of periodontitis need not be derived only from periodontitis-focused research. Much is to be gained from research progress in other chronic inflammatory conditions. Studies are ongoing to evaluate the role of other proinflammatory cytokines in the pathophysiology of conditions similar to periodontitis, such as RA, Crohn's disease and IBD, and to develop antibodies which specifically target these cytokines for novel future treatment strategies. IL-21, a new member of the type 1 cytokine superfamily, promotes osteoclastogenesis in RA (Ref. 215) and has been suggested as target for immune-mediated diseases, especially for preventing bone destruction (Ref. 216). IL-23, a member of the IL-12 family, has been reported to be involved in osteoclastogenesis via induction of RANKL expression. Treatment with the IL-12p40 monoclonal antibody Ustekinumab against the common p40 subunit of IL-12 and IL-23, which thereby neutralises IL-12 and IL-23, has shown clinical efficacy in patients with Crohn's disease (Ref. 217) and psoriatic arthritis (Ref. 218). Currently, numerous IL-23 receptor antagonists are reported to be under development in clinical or preclinical studies (Refs 219, 220).

As discussed throughout this review, research into the molecular pathogenesis of periodontitis is continuously producing novel and significant results. Despite extensive research, however, the detailed mechanisms of the pathogenesis of periodontitis are still not elucidated. Nevertheless, the field is moving forward, utilising technological advances and synergy effects from findings in closely related diseases. Periodontitis is currently being connected to the pathogenesis of various systemic diseases and conditions, further emphasising the importance of a deeper understanding of this common condition. Progress in the understanding of periodontal disease may enable adjunctive treatments focused on modulating the host response. Successful novel treatment strategies have the potential to improve both the oral and the systemic health of patients afflicted with periodontitis.

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Features associated with this article

Figures

Figure 1. Characteristics of periodontitis.
Figure 2. Schematic overview of the pathogenesis of periodontitis.
Figure 3. Inflammatory mediators in the pathogenesis of periodontitis.

Table

Table 1. Cytokine levels in the gingival crevicular fluid and in gingival tissue.

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