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Inflammatory and immune pathways in the pathogenesis of periodontal disease

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Inflammation is the physiological response to a variety of injuries or insults, including heat, chemical agents or bacterial infection. In the acute phase of inflammation, the response is rapid and of short duration. If the insult or injury is not resolved, the response becomes chronic, which can be considered as nonphysiologic or pathologic. When inflammation becomes chronic, the adaptive immune response is activated with involvement of the cellular and non-cellular mechanisms of acquired immunity. Immune mechanisms play further roles in the resolution of inflammation and in the healing process, including the repair and the regeneration of lost or damaged tissues. Thus, innate (inflammatory) immunity and acquired immunity must be coordinated to return the injured tissue to homeostasis (85).

The etiology of periodontal diseases is bacteria. The human oral cavity harbors a substantial and continuously evolving load of microbial species. The ecological interactions between the host and microbes determine the severity of the disease. Unlike many infectious diseases, periodontal diseases appear to be infections mediated by the overgrowth of commensal organisms, rather than by the acquisition of an exogenous pathogen. As microorganisms evolve more rapidly than their mammalian hosts, immune mechanisms that determine the ecological balance of commensal organisms also need to change to preserve homeostasis (65).

Knowledge of how immune mechanisms and inflammatory responses are regulated is critical for understanding the pathogenesis of complex diseases, such as periodontitis. The pathogenesis of periodontal diseases is mediated by the inflammatory response to bacteria in the dental biofilm (Fig. 1). However, identification of the true ‘pathogens’ in periodontitis has been elusive. There is evidence that specific microbes are associated with the progressive forms of the disease; however, the presence of these microorganisms in individuals with no evidence of disease progression suggests that the disease is the net effect of the immune response and the inflammatory processes, not the mere presence of the bacteria. Regulation of immune–inflammatory mechanisms governs patient susceptibility and is modified by environmental factors (219, 220, 241). This review will address the pathways of inflammation in periodontal diseases by focusing on immunologic mechanisms to elucidate sites of regulation. Clinical features of the periodontal diseases are beyond the scope of this work but are within the context of the pathogenic mechanisms. Possible clinical outcomes will be discussed in relation to the inflammatory–immunologic changes throughout the disease process.

Periodontal diseases: what do we know?

There are two common diseases affecting the periodontium. The first is gingivitis, which is defined as inflammation of the gingiva in which the connective tissue attachment to the tooth remains at its original level. The disease is limited to the soft-tissue compartment of the gingival epithelium and connective tissue (12). The second is periodontitis, which is an inflammation of the supporting tissues of the teeth with progressive attachment loss and bone destruction (55). Both diseases and their symptoms are very common in populations worldwide. In the USA, adolescents have gingivitis and signs of gingival bleeding, whereas 54% of the adult population in the USA exhibits gingival bleeding (99). Thirty-seven per cent of the adult population in the USA suffers from severe periodontitis (160). In both cases, the disease is associated with the accumulation of bacteria at the dento–gingival margin, while the causal relationship of specific organisms is not fully clear. The host responds to microbial challenge by generating an inflammatory cell infiltrate in the tissue subjacent to the periodontal pocket (186).

The initial inflammation in the periodontal tissues should be considered a physiologic defense mechanism against the microbial challenge, rather than pathology. The clinical findings of the disease at this stage include supragingival and subgingival plaque formation, which are usually accompanied by calculus formation and gingival inflammation (154). If plaque is removed, there is resolution with return to homeostasis; if the lesion persists, it becomes pathology. For convenience, we will use the well-known stages of gingivitis and periodontitis, described by Page & Schroeder, in 1976 (186), for descriptive purposes: the initial lesion; the early lesion; the established lesion; and the advanced lesion. The advanced lesion is also called the destructive phase, because it represents the transition from gingivitis to periodontitis. What makes inflammation and immunologic events underlying periodontal diseases confusing is that the immunologic events overlap in different phases of disease. It should be emphasized that division of the immune response into various systems, such as innate immunity and adaptive immunity, is a rather arbitrary distinction imposed by immunologists (12). Although it is easier to describe the inflammation in compartments, the mechanisms involved in inflammation, resolution and healing include all components of the immune system that interact cooperatively to protect the periodontium (266). It is important to bear in mind that as the lesion progresses, the preceding pathways still function.

The initial lesion is the response of resident leukocytes and endothelial cells to the bacterial biofilm. At this stage, there are no signs of clinical inflammation, but the changes in the tissues can be observed histologically. The metabolic products of bacteria trigger junctional epithelium cells to produce cytokines and stimulate neutrons to produce neuropeptides, which cause vasodilatation of local blood vessels. Neutrophils leave the vessel and migrate toward the site of inflammation in response to chemokines. The early lesion follows, with increased numbers of neutrophils in the connective tissue and the appearance of macrophages, lymphocytes, plasma cells and mast cells. Complement proteins are activated. The epithelium proliferates to form rete pegs, observed histologically, and clinical signs of gingival inflammation, such as bleeding, can be seen. Gingival crevice fluid flow is increased.

The following stage is the established lesion. This can be considered as the period of transition from the innate immune response to the acquired immune response. Macrophages, plasma cells, and T and B lymphocytes are dominant, with IgG1 and IgG3 subclasses of B lymphocytes also present. Blood flow is impaired, and the collagenolytic activity is increased. There is also increased collagen production by fibroblasts. Clinically, this stage is a moderate to severe gingivitis with gingival bleeding and color and contour changes. The final stage is the transition to periodontitis: the advanced lesion. Irreversible attachment loss and bone loss are observed histologically and clinically. The inflammatory lesion extends deeper, affecting the alveolar bone (51).

Cells and mediators of periodontal inflammation

The innate immune system includes cells of nonhematopoietic origin, especially epithelial cells; myeloid cells of hematopoietic origin (phagocytes); and the innate humoral defense, the complement cascade (266). Neuropeptides contribute to this initial, immediate response to microbial challenge (236). The initial response, acute inflammation, is the physiologic response to the microbial challenge to recruit adequate cells to sites of infection through the production of cytokines and chemokines (Fig. 1). If the infection fails to clear, the chronic lesion is initiated with transition to the early lesion. Still an innate immune response pathways are stimulated that will activate the adaptive immune response. Innate immunity was formerly thought to be nonspecific, characterized by the phagocytosis and digestion of microorganisms and foreign substances by macrophages and neutrophils (97, 166). Phagocytes such as macrophages and neutrophils have surface receptors that recognize and bind surface molecules of bacteria (266). These pattern recognition receptors, including the toll-like receptors, distinguish between the host and the bacteria (197). After recognition of microorganisms and foreign substances, chemokines are secreted to attract phagocytes. The complement system also generates biologically active proteins, including the anaphylotoxins C3a, C4a and C5a that attract the different host immune cells monocytes, lymphocytes and neutrophils, respectively. Complement proteins can also directly kill certain bacteria. Histamine-induced vasodilatation by mast cells increases blood flow and recruitment of phagocytes.

Complement

The complement cascade can be activated through three pathways: the classical pathway; the lectin pathway; and the alternative pathway.

The classical pathway is activated by immunoglobulin – IgG or IgM – which binds the first complement protein, C1q, to a domain on its Fc tail. Bound C1q binds other C1 proteins to form a complex, C1qrs, which initiates a series of enzymatic reactions, cleaving C4 to C4a and C4b, and C2 to C2a and C2b. C4b and C2a become part of the C1 complex, forming a C3 convertase that cleaves C3 to C3a and C3b. C3b binds to the bacterial surface and, with several accessory proteins, forms a new enzyme to cleave C5 to C5a and C5b. C5b interacts with the terminal complement proteins, C6 to C9, to form the membrane attack complex that inserts C8 and C9 into the bacterial membrane, forming pores to disrupt the membrane.

The lectin pathway employs a mannose-binding lectin to bind carbohydrate on the bacterial cell-surface to form mannose-associated serine protease-2. This molecule has the capacity to interact with the complement proteins C4 and C2 to convert C3 to C3a and C3b, as in the classical pathway.

The alternative pathway is activated by bacterial polysaccharides, such as zymosan, lipopolysaccharide or aggregated IgA, through factor P (properdin) to cleave C3. C3b, and factors B and D convert C5 into C5a and C5b and the cascade continues to completion.

Both gingivitis and chronic periodontitis have been characterized primarily as activators of the alternative pathway. This is of some interest because it suggests that even though pathogen-specific antibodies are formed in chronic periodontitis, most of the complement activation in this disease is still via the alternative pathway (256). It is also known that other than these very well-studied pathways, there are proteins that can interact directly with C3 and C5: plasmin can cleave C3 into C3a and C3b; and thrombin has the ability to cleave C5.

Neuropeptides

During the innate immune response to periodontal pathogens, another element of the human defense system is also activated. Neurons generate electric impulses in response to chemical or mechanical stimuli, conduct the impulse and translate the electrical activity into a chemical signal. Alternatively, peptide neurotransmitters – neuropeptides – can be secreted into the extracellular fluid, where they act locally through receptors on other neurons or immune cells. Most neuropeptides act on nonneuronal targets (90), such as receptors for substance P and calcitonin gene-related peptide, found on immune cells, suggesting that the paracrine action of neuropeptides has important immunomodulatory roles (80, 150, 165) (Fig. 1). Recently, the nervous system has been identified as a critical regulator of inflammation in periodontal diseases (236). Furthermore, under pathological conditions some neuropeptides are synthesized and released from inflammatory cells (168). Therefore, the identification of neuropeptide receptors on immune cells suggests that communication exists between the immune and neurological systems, which may result in modulation of the inflammatory response (80, 165). Neuropeptides signal nonneuronal cells through G protein-coupled receptors located on the cell membrane (150). Vanilloid receptor-1, a neuropeptide receptor, is upregulated in inflammatory bowel disease, suggesting a possible role of this receptor in chronic inflammation (262).

The contribution of the nervous system to inflammation is not limited to vasodilatation and immune-cell recruitment. Cytokines and other products of immune cells can modulate the action, differentiation and survival of nerve cells, while neuropeptides released from neurons play pivotal roles in influencing the immune response. The interaction relies on the receptor-sensitizing characteristics of the cytokines. When a cytokine engages a neuron receptor, it initiates the release of neuropeptides (184). The discovery of protease-activated receptors revealed that protease-activated receptor 2 has an especially important role in chronic inflammation (246). Protease-activated receptor 2 is co-expressed with substance P and calcitonin gene-related peptide on sensory nerves, where it is believed to mediate inflammation (53, 222) (Fig. 1). In addition, cytokines have been shown to regulate the expression of substance P and to facilitate the lipopolysaccharide-induced release of

calcitonin gene-related peptide in sympathetic neurons (92, 113). Also, calcitonin gene-related peptide enhances interleukin-1-induced accumulation of neutrophils and induces T-cell cytokine secretion (26, 137). Neural growth factor has been shown to directly regulate the synthesis of calcitonin gene-related peptide by B-cells as it does in sensory neurons (22). In the course of inflammation, kininogens are degraded to form kinins, including bradykinin, which together are important mediators of inflammation. Kinins are known to be proinflammatory, leading to vasodilatation, plasma extravasation and the release of other inflammatory mediators, notably the neuropeptides substance P and calcitonin gene-related peptide (67).

With the identification of neuropeptides in gingival crevice fluid, it is becoming increasingly evident that periodontitis and other orofacial inflammatory disorders may be modulated by imbalances in certain neuropeptides (78, 141, 142, 151, 152). In addition to the presence of neuropeptides in gingival crevice fluid, fibers innervating the periodontal tissues in humans have been shown to be immunoreactive to a number of neuropeptides, including substance P, calcitonin gene-related peptide, vasoactive intestinal peptide and neuropeptide Y (153).

The major function of neuropeptides in inflammation is vasodilatation, vasoconstriction and the recruitment and regulation of immune cells (6, 28, 126). Three major neuropeptides have modulatory effects in periodontal inflammation: substance P, calcitonin gene-related peptide and vasoactive intestinal peptide.

Substance P

Substance P is a member of the tachykinin family of neuropeptides, also known as the neurokinins (150). Substance P evokes a rapid response upon release and causes increased microvascular permeability, edema formation and subsequent plasma protein extravasation. Vasodilatation caused by substance P occurs indirectly by stimulating histamine release from mast cells (29, 150). Accordingly, edema induced by substance P is primarily caused by increased vascular permeability mediated through its action on neurokinin 1 receptors on endothelial cells (136). Several studies have shown the presence of substance P in human gingival tissues and in gingival crevice fluid (11, 151). The levels of substance P in the gingival crevice fluid are reduced after periodontal treatment, supporting the view of a local source of tachykinins in the gingival tissues (151).

The actions of substance P on immune cells are also important. Substance P limits the production of transforming growth factor beta by macrophages (161) and induces the synthesis of interleukin-6 by monocytes (140). Interestingly, substance P is also synthesized by immune cells. Sources of substance P, in addition to neurons, include monocytes, dendritic cells, eosinophils, T-lymphocytes and mast cells (130, 150). Mononuclear phagocytes and dendritic cells produce substance P when activated with lipopolysaccharide *in vitro* (131).

Calcitonin gene-related peptide

Calcitonin gene-related peptide has potent vasodilator activity and is frequently co-localized with substance P, which has been shown to regulate the vasodilator activity of calcitonin

gene-related peptide (23, 38). In addition to its known vasodilator activity, calcitonin gene-related peptide has immunosuppressive actions that down-regulate the inflammatory response (232), such as suppressing interleukin-2 production and the proliferation of murine T-cells (252). It inhibits hydrogen peroxide production by macrophages in response to interferon gamma and presenting antigen (177, 185). Calcitonin gene-related peptide also impacts bone metabolism, thus inhibiting osteoclastic bone resorption and stimulating osteogenesis (123).

Vasoactive intestinal peptide

Vasoactive intestinal peptide is an important immune-modulatory peptide that is capable of regulating the production of both proinflammatory and anti-inflammatory mediators (15, 57, 193). The major nonneuronal sources of vasoactive intestinal peptide are neutrophils and mast cells (36, 178). While vasoactive intestinal peptide inhibits lipopolysaccharide-induced production of tumor necrosis factor alpha, interleukin-6 and interleukin-12 in activated macrophages, it stimulates the production of the potent anti-inflammatory cytokine, interleukin-10, and suppresses T-cell proliferation (57). The levels of vasoactive intestinal peptide are significantly elevated in periodontitis sites compared with clinically healthy sites, and nonsurgical periodontal treatment results in a clinical improvement along with a concomitant reduction in the levels of vasoactive intestinal peptide (142).

Toll-like receptors

In the oral epithelium, complementary defense mechanisms are present. Epithelial cells have tight intercellular junctions that impede the entry of bacteria and their metabolites. Lipopolysaccharide is a cell-wall component of all gram-negative microorganisms (197). Once exposed to lipopolysaccharide, a series of complex mechanisms are triggered, which lead to extracellular matrix degradation and the initiation of osteoclastogenesis. The main function of dendritic cells is presentation of antigen to other cells of the immune system. Recognition of innate immune signals by dendritic cells relies on a limited number of pathogen-related receptors. These include toll-like receptors and related proteins that regulate apoptosis, inflammation and immune responses (3, 95) (Fig. 1).

The toll-like receptors family of proteins is the best-characterized class of pattern-recognition receptors. Dendritic cells express toll-like receptors, and different dendritic-cell subsets express distinct toll-like receptors that are associated with particular functions in innate responses and the generation of distinct T-cell subsets (98, 103). Toll-like receptors are also expressed on lymphocytes and osteoclast precursors, as well as on macrophages, osteoblasts and stromal and epithelial cells, each of which has different toll-like-receptor expression profiles (83, 96, 107, 228). Toll-like receptors are unique receptors that recognize molecules that are broadly shared by microorganisms, but are distinguishable from host molecules; these are collectively referred to as ‘pathogen-associated molecular patterns’. Toll-like receptors detect multiple pathogen-associated molecular patterns, including lipopolysaccharide, bacterial lipoproteins and lipoteichoic acids, flagellin, CpG DNA of bacteria and viruses, double-stranded RNA and single-stranded viral RNA (96). To date, 11 different toll-like-receptor molecules have been identified in human periodontal tissues, and

their expression, distribution and ligand specificities have been characterized (125, 145, 195, 228) (Table 1).

When toll-like receptors bind pathogen-associated molecular patterns, a series of intracellular events are initiated, leading to the production of cytokines, chemokines and antimicrobial peptides (104). The toll-like-receptor domain can bind four different adapter proteins and has the potential to induce various cytokines through nuclear factor of kappa light polypeptide gene enhancer in B-cells pathways in the nucleus of the cell. Known adapter proteins of toll-like receptors are myeloid differentiation primary response protein (Myd88), toll / interleukin-1 receptor domain-containing adapter protein, toll / interleukin-1 receptor domain containing adapter-inducing interferon beta and toll / interleukin-1 receptor domain containing adapter-inducing interferon beta-related adapter molecule. Different toll-like receptors induce different responses. For example, in dendritic cells, the interaction of toll-like receptor 4 and lipopolysaccharide results in the production of proinflammatory cytokines such as interleukin-12, and the interaction of toll-like receptor 3 with lipopolysaccharide results in the production of type-I interferon. It is known that toll-like receptor 2 and toll-like receptor 4 predominate in periodontal tissues (82). Interestingly, the same toll-like receptor can trigger different responses depending upon the intracellular adapter protein. For example, when lipopolysaccharide binds to toll-like receptor 4 and uses myeloid differentiation primary response protein (MyD88) and toll / interleukin-1 receptor domain-containing adapter protein as adapters, the result is the production of tumor necrosis factor alpha, interleukin-6 and interleukin-12. If the adapters toll / interleukin-1 receptor domain-containing adapter-inducing interferon beta-related adapter molecule and toll / interleukin-1 receptor domain-containing adapter-inducing interferon beta with the same toll-like receptor type are used, release of interferon alpha / beta and activation of interferon regulatory factor 3 follows (1, 35, 107, 125, 253).

Toll-like receptors 1, 2, 4, 5 and 6 recognize mainly products that are unique to bacteria and not made by the host. This gives them the specificity to differentiate microorganisms from the host (96). Recognition by toll-like receptor pathways is a crucial phase in inflammation. For a complete review of toll-like receptors and their pathways, see Uehara & Takada (239).

Antigen presentation and activation of acquired immunity

If the early lesion persists without resolution, bacterial antigens are processed and presented by lymphocytes, macrophages and dendritic cells. Broadly, two different subsets of lymphocytes have evolved to recognize extracellular and intracellular pathogens after being presented with antigens by the innate immune cells: T-lymphocytes and B-lymphocytes. B-lymphocytes bear immunoglobulin molecules on their surface, which function as antigen receptors. Antibody, which is a soluble form of immunoglobulin, is secreted following activation of B-cells to bind pathogens and foreign material in the extracellular spaces (humoral immunity). T-cells are the effectors of cell-mediated immunity (delayed hypersensitivity). The T-cell antigen receptor is a membrane-bound molecule, similar to immunoglobulin, which recognizes peptide fragments of pathogens. Activation of the T-cell receptor requires the major histocompatibility complex, which is also a member of the immunoglobulin superfamily. Two classes of major histocompatibility complex molecules

are required for the activation of distinct subsets of T-cells. Various T-cell subsets kill infected target cells and activate macrophages, B-cells and other T-cells. Thus, T-cells are essential for the regulation of both humoral and cell-mediated responses.

Classically, T-lymphocytes have been classified into subsets based on the cell-surface expression of CD4 or CD8 molecules. $CD4^+$ T-cells (T-helper cells) were initially subdivided into two subsets, designated T-helper 1 and T-helper 2, on the basis of their pattern of cytokine production (172). T-helper 1 cells secrete interleukin-2 and interferon gamma, whereas T-helper 2 cells produce interleukins 4, 5, 6, 10 and 13. Both cell types produce interleukin-3, tumor necrosis factor alpha and granulocyte–macrophage colony-stimulating factor (112, 266). The major role of the T-helper 1 cytokines interleukin-2 and interferon gamma is to enhance cell-mediated responses, whereas the T-helper 2 signature cytokine, interleukin-4, suppresses cell-mediated responses (170). T-cell subsets are also important in the behavior of B-cells. For example, T-helper 1 cells direct B-cell secretion of IgG2, whereas T-helper 2 cells up-regulate IgG1 secretion. CD8 T-cells (cytotoxic T-cells) are immune effector cells that also secrete cytokines which are characteristic of either T-helper 1 or T-helper 2 cells (266).

More recent studies have described two new well-defined CD4 T-cell subsets, T-helper 17 and T-regulatory T-cells, which play antagonistic roles as effector and suppressor cells, respectively (4, 207, 254). T-helper 17 cells are named for their unique production of interleukin-17. T-helper 17 cells also produce interleukin-22. T-helper 17 lymphocytes, like T-helper 1 cells, are also noted for their stimulatory role in osteoclastogenesis (258). T-helper 17 cells are observed in chronic periodontitis sites, and T-helper 17-related cytokines are produced in periodontal lesions (180, 226, 247).

T-regulatory cells have a protective role in periodontal tissue damage. Natural T-regulatory cells are CD4- and CD25-expressing T-cells that specifically regulate the activation, proliferation and effector functions of activated conventional T-cells (4, 14, 207). T-regulatory cells are found in periodontal disease sites (30, 175). The cytokines produced by T-regulatory cells are transforming growth factor beta and T-lymphocyte-associated molecule 4 (cytotoxic T-lymphocyte antigen 4), which down-regulate inflammation. Interleukin-10, transforming growth factor beta and cytotoxic T-lymphocyte-associated antigen 4 are reported to decrease periodontal disease progression (30).

New data suggest the existence of an antigen-presenting cell type from the follicular Th-cell lineage that produces interleukin-21 (118). This type of antigen-presenting cell is characterized by the expression of the chemokine receptor, chemokine (C-X-C motif) receptor 5 (24, 50, 211).

The other important antigen-presenting cell is the macrophage. Macrophages, which are phagocytic cells from the myeloid lineage, efficiently ingest particulate antigen and express the major histocompatibility complex class II molecules to induce costimulatory activity on T-cells. Macrophages are widely distributed cells that play an indispensible role in homeostasis and defense. Macrophages can be phenotypically polarized by the microenvironment. The classic inflammatory macrophage (M1) is activated by interferon

gamma and lipopolysaccharide. Alternatively activated macrophages (M2) are important cells in the resolution of inflammation; they have reduced capacity to produce proinflammatory cytokines (18).

The transition from the established lesion, dominated by T- and B-cells, to the advanced lesion (progressive periodontitis) is not well understood. We know that dendritic cells also express the major histocompatibility complex class II molecules and have costimulatory activity. The unique ability of B-cells to bind and internalize antigens via their immunoglobulin receptors may be important in activating T-lymphocytes, pointing out that costimulatory molecules are present on B-cells. Costimulation can be thought of as the mechanism by which antigen-presenting cells inform T-cells that the antigen requires a proliferative response preventing T-cell apoptosis or anergy (266). It has become clear that CD4 T-cells and certain innate immune cells, such as dendritic cells, monocytes and neutrophils, are in perfect communication through cytokine networks (7, 66, 108, 220, 231).

It is evident that innate and adaptive systems are coordinately involved in the inflammatory response and tissue destruction, although we lack a complete understanding of the mechanism. In the case of periodontal disease, where all elements of the immune system are involved, inflammatory mechanisms and signals are dysregulated. For instance, T-cells extracted from diseased periodontal tissues exhibit a reduced response to stimuli, which suggests that the cell-mediated response is suppressed in patients with periodontal disease (34); following periodontal therapy, lymphocyte reactivity has been reported to return to normal (225).

Activation of B-cells is an important step in the maturation of the antibody response. This event is mediated mainly by the tumor necrosis factor family of proteins and their receptors. In addition to their role in presenting antigen, B-cells also function as effectors, through cytokine secretion, lysosomal components, reduced oxygen metabolites, nitric oxide and antibodies. This is also important because in severe periodontal lesions, B-cells are the predominant antigen-presenting cells, suggesting that B-cell antigen presentation may allow further activation and clonal expansion of already activated T-cells (63, 266).

The role of antibody and cell-mediated immunity in the pathogenesis of periodontal diseases is beyond the scope of this review. For a recent detailed review of acquired immune mechanisms in periodontitis, see Berglundh & Donati (17). The role of cytokines and other mediators from cells of the acquired immune network is discussed in subsequent sections of this review.

Cytokines and chemokine networks

Cytokines and chemokines (chemotactic cytokines) are the messages between cells. The immune response to infection is regulated by cytokine and chemokine signals. Cytokines are low-molecular-weight proteins involved in the initiation and further stages of inflammation, in which they regulate the amplitude and the duration of the response. The genetic regulation leading to the secretion of proinflammatory cytokines from a variety of cells is generally dependent on the activation of nuclear factor kappa-B transcription (8, 75). The nuclear

factor kappa-B regulated pathways are activated by pathogen-associated molecular patterns, such as lipopolysaccharide, through the toll-like receptor pathway (75).

Cytokines are produced by resident cells, such as epithelial cells and fibroblasts, and by phagocytes (neutrophils and macrophages) in the acute and early chronic phases of inflammation, and by immune cells (lymphocytes) in established and advanced lesions (5). After recognition and presentation of microbes to the appropriate cells, cytokines of the innate response, including tumor necrosis factor alpha, interleukin-1beta and interleukin-6, are the first to appear in the periodontal disease pathogenesis pathways (58). Interleukin-1beta and interleukin-6 are signature innate cytokines and have been characteristically associated with inflammatory cell migration and osteoclastogenesis (56, 73). Tumor necrosis factor alpha is a multi-effect cytokine that has many functions, from cell migration to tissue destruction. Tumor necrosis factor alpha impacts cell migration by inducing the up-regulation of adhesion molecules to promote rolling and adhesion of neutrophils to the vessel wall, leading to extravasation. It also stimulates the production of chemokines involved in cell migration to infected and inflamed sites (42, 117, 190, 251). Tumor necrosis factor alpha upregulates the production of interleukin-1beta and interleukin-6 (42, 59, 73, 128, 173, 182, 251). Tumor necrosis factor alpha is also correlated with extracellular matrix degradation and bone resorption through actions promoting the secretion of matrix metalloproteinases and RANKL (62, 72, 73) and coupled bone formation (13). Accordingly, experimental periodontitis in tumor necrosis factor alpha p55 receptor-deficient mice was characterized by a significant decrease in matrix metalloproteinase and RANKL expression and resistance to periodontitis (59).

Chemokines are chemotactic cytokines that play a very important role in the migration of phagocytic cells to the site of infection. Once blood leukocytes exit a vessel, they are attracted, by functional gradients of chemotactic factors, to the site of infection (200, 267). Chemokines are synthesized by a variety of cells including endothelial, epithelial and stromal cells, as well as leukocytes. Functionally, chemokines can be grouped as homeostatic or inflammatory (171). In addition to their cell-trafficking role, chemokines provide messages leading to other biological processes, such as angiogenesis, cell proliferation, apoptosis, tumor metastasis and host defense (48, 171, 200, 201, 267). Bacterial peptides are also chemotactic for inflammatory cells, but the discussion herein will focus upon host-derived chemokines.

Chemokines are small, heparin-binding proteins ranging from 7 to 15 kDa. They are classified into four subfamilies according to the configuration of cysteine residues near the N-terminus. The nomenclature is as follows: chemokines are designated CXC and CX3C if two cysteines are separated and as CC and C if they are not. Their receptors are named by adding ‘R’ to the end of the particular chemokine, for example, ‘CXCR’ or ‘CCR’. Detailed information on the classification codes, the designated names of the chemokines, their receptors and the target cells they are affecting is presented in Table 2 (21, 37, 64, 74, 101, 110, 146, 147, 200, 208, 209, 249, 264, 267). Binding of a chemokine to its respective receptor initiates the cell-migration process, beginning with integrin-dependent adhesion and diapedesis. Chemokines target leukocytes of the innate immune system, as well as lymphocytes of the adaptive immune system (233).

The first cytokine identified to have chemotactic activity was interleukin-8 / chemokine (C-X-C motif) ligand 8. In the periodontium, this cytokine is produced primarily by gingival fibroblasts, gingival epithelial cells and endothelial cells (227, 229, 265). Interleukin-8 is a polymorphonuclear leukocyte chemoattractant. It is detectable in healthy and diseased periodontal tissues and has been associated with subclinical inflammation of the initial lesion, which is comprised of polymorphonuclear neutrophils (163, 188, 263). Interleukin-8 / chemokine (C-X-C motif) ligand also has an important role in bone metabolism. It has direct actions on osteoclast differentiation and activity by signaling through the specific receptor, chemokine (C-X-C motif) receptor 1 (16).

Another crucial chemokine of innate immunity is macrophage chemotactic protein-1 / chemokine (C-C motif) ligand 2. Macrophage chemotactic protein-1 mediates the recruitment of monocytes / macrophages, the second wave of the innate response to bacteria (76, 183). Macrophage inflammatory protein 1 alpha / chemokine (C-C motif) ligand 3 is the most abundantly expressed chemokine in periodontitis tissues, with its expression localized in the connective tissue subjacent to the pocket epithelium of inflamed gingival tissues. Together with regulated and normal T cell expressed and secreted / chemokine (C-C motif) ligand 5, macrophage inflammatory protein 1 alpha / chemokine (C-C motif) ligand 3 may also be involved in the migration of macrophages to periodontal tissues (64, 102). Chemokine (C-X-C motif) receptor 3 and its ligand, interferon gamma-induced protein 10 / chemokine (C-X-C motif) ligand 10, are also expressed in diseased periodontal tissues, (61, 102) and are associated with higher levels of interferon gamma in inflammation. Chemokine (C-C motif) receptor 4 is expressed at higher levels in chronic periodontitis and it is associated with higher levels of interleukin-4 and interleukin-10 in the periodontium (61, 62).

It has become increasingly clear that chemokines are multipurpose ligands in mediating repair and angiogenesis. The time and the place of secretion are of utmost importance. In a study by DiPietro et al., macrophage chemotactic protein-1 / chemokine (C-C motif) ligand 2-deficient mice demonstrated delayed wound re-epithelialization (43, 149). Chemokines are equally crucial in guiding adaptive immunity and also play a critical role in bone metabolism. For instance, chemokines such as macrophage-derived chemokine / chemokine (C-C motif) ligand 22, thymus and activation-regulated chemokine / chemokine (C-C motif) ligand 17 and I-309 / chemokine (C-C motif) ligand 1 attract T-helper 2 and T-regulatory cells binding to chemokine (C-X-C motif) receptor 4 and chemokine (C-X-C motif) receptor 8, respectively (37, 74, 208). It has been suggested that the expression of T-helper 2 and T-regulatory cell chemoattractants, such as macrophage-derived chemokine / chemokine (C-C motif) ligand 22, thymus and activation-regulated chemokine / chemokine (C-C motif) ligand 17 and I-309 / chemokine (C-C motif) ligand 1, reduce periodontal disease severity (175). B cell-attracting chemokine 1 / chemokine (C-X-C motif) ligand 13, an important B-cell chemoattractant, is expressed in diseased tissues, suggesting a role for the accumulation of these cells in the periodontium. The expression of B cell-attracting chemokine 1 / chemokine (C-X-C motif) ligand 13 may be important in the local humoral response to periodontal pathogens (119).

Chemokines are involved in both the physiology and the pathology of bone metabolism. They are essential signals for the trafficking of osteoblast and osteoclast precursors, and consequently as potential modulators of bone homeostasis (16, 257). The chemokines implicated in regulating bone metabolism are identified through expression of receptors including chemokine (C-C motif) receptors 1 and 2, and chemokine (C-X-C motif) receptors 3 and 4; these receptors are expressed on osteoclast precursors, mature osteoclasts and osteoblasts. The potential chemokine ligands include stromal cell-derived factor-1 / chemokine (C-X-C motif) ligand 12, macrophage inflammatory protein 1 alpha / chemokine (C-C motif) ligand 3, regulated and normal T cell expressed and secreted / chemokine (C-C motif) ligand 5, macrophage inflammatory protein 1 gamma / chemokine (C-C motif) ligand 9, macrophage chemotactic protein-1 beta / chemokine (C-C motif) ligand 2, macrophage chemotactic protein-3 / chemokine (C-C motif) ligand 7, monokine induced by gamma interferon / chemokine (C-X-C motif) ligand 9 and transcript variant CKβ8 / chemokine (C-C motif) ligand 23 (115, 116, 127, 134, 183, 249, 257, 259, 264). Interferon gamma-induced protein 10 / chemokine (C-X-C motif) ligand 10 induces osteoblast proliferation through chemokine (C-C motif) receptor 3 (71, 143), while stromal cell-derived factor-1 alpha / chemokine (C-X-C motif) ligand 12 and B cell-attracting chemokine 1 / chemokine (C-X-C motif) ligand 13 induce both proliferation and collagen type I mRNA expression in osteoblasts through chemokine (C-C motif) receptors 4 and 5 (144). In addition to a role in osteoclastogenesis, chemokines also impact osteoclast functions. Stromal cell-derived factor-1 alpha / chemokine (C-X-C motif) ligand 12 increases the activity of matrix metalloproteinase 9 in human osteoclasts, resulting in increased bone resorption (70).

There is some evidence that regulated and normal T cell expressed and secreted / chemokine (C-C motif) ligand 5 acts on osteoblasts, resulting in chemotaxis and promoting cell survival (260). Interestingly, RANKL also induces the production of macrophage chemotactic protein-1 / chemokine (C-C motif) ligand 2, macrophage inflammatory protein 1 / chemokine (C-C motif) ligand 3, regulated and normal T cell expressed and secreted / chemokine (C-C motif) ligand 5 and monokine induced by gamma interferon / chemokine (C-X-C motif) ligand 9 by osteoclasts, suggesting a coupling contribution to bone resorption (115). Taken together, these studies suggest that chemokines can effectively contribute to bone remodeling by driving osteoblast migration and activation.

Interferon gamma is a signature cytokine of the adaptive immune response. Its main function is to promote antigen-presenting cell binding of antigen by up-regulating major histocompatibility complex class I and class II expression (199, 238). Interferon gamma also plays a major role in B-cell maturation, and, accordingly, in immunoglobulin secretion (179). In periodontal disease, interferon gamma is present at high levels in periodontal lesions, and is associated with progressive lesions or severe forms of periodontitis (46, 61, 88).

Interleukin-4 is another important adaptive-immunity cytokine that induces proliferation of T-cells and regulates B-cell immunoglobulin secretion. It is considered an anti-inflammatory cytokine. Interleukin-4 has known antitumor actions. Interleukin-4 inhibits the activity of proinflammatory cytokines, such as the interleukin-2-induced generation of natural killer cells and the activation of macrophages (179). Interleukin-4 can also block nitric oxide

generation by macrophages (170). Studies also suggest that interleukin-4 down-regulates the production of other cytokines, including interleukin-1beta, tumor necrosis factor alpha and interleukin-6, by human peripheral blood monocytes and T-helper 1 cells (44, 49), inhibiting the transcription of these proinflammatory cytokines and interferon gamma. Additionally, interleukin-4 inhibits the production of matrix metalloproteinases and RANKL, and concomitantly induces the up-regulation of tissue inhibitor of metalloproteinases and osteoprotegerin (93, 204), reinforcing its potential protective role in periodontal diseases (68). Interleukin-4 also induces the production of interleukin-10, another anti-inflammatory cytokine (191). Interleukin-10 plays a major role in suppressing immune responses by inhibiting the antigen-presenting capacity of macrophages (40, 52). Interleukin-10 is a potent effector for activated human B-cells (202). It is widely expressed in inflamed periodontal tissues, where it is thought to limit disease severity (60, 62, 133). Interleukin-10 interferes directly with the production of interferon gamma and interleukin-17 by T-helper 17 cells (100, 176). Interleukin-10 plays a direct protective role in tissue destruction by down-regulating both matrix metalloproteinases and RANKL. Interleukin-10 characteristically induces the up-regulation of tissue inhibitor of metalloproteinases, which inhibit the matrix metalloproteinase family of proteins (31, 33, 62).

Interleukin-12 was originally described as a factor that promotes the activity of natural killer cells and CD8 T-cells (132). It has the capacity to enhance T-cell and natural killer cell proliferation after activation by other stimuli (121, 189). Natural killer cells appear to be most effective at preventing early infection, but T- and B-cells and their products are required to resolve the infection (9). Interleukin-4 and interleukin-10 are powerful inhibitors of the production of interleukin-12. It has been suggested that these two cytokines may determine the balance between T-helper 1 and T-helper 2 cells in the periodontal lesion (237).

Interleukin-13 is another potent modulator of human monocyte / macrophage and B-cell function. Monocyte / macrophage cell-surface major histocompatibility complex class II and several integrin molecules are up-regulated by interleukin-13 (39). The monocyte / macrophage-related production of interleukin-1alpha, interleukin-1beta, interleukin-6, interleukin-8 and tumor necrosis factor alpha is inhibited by interleukin-13, and interleukin-1 receptor antagonist secretion is enhanced (39, 269) suggesting an anti-inflammatory role along with interleukin-4 and interleukin-10 (269).

Transforming growth factor beta is a growth factor that regulates cell growth, differentiation and matrix production, and is also a potent immunosuppressive factor that down-regulates the transcription of proinflammatory factors (such as interleukin-1beta and tumor necrosis factor alpha) and matrix metalloproteinases (181, 223). In active periodontal lesions, the levels of transforming growth factor beta are negatively correlated with the levels of RANKL, reinforcing its protective role against tissue destruction (45, 46, 223).

Lipid mediators of inflammation

Prostaglandins are derived from the hydrolysis of membrane phospholipids. Phospholipase A_2 cleaves the sn-2 position of membrane phospholipids to generate arachidonic acid, a

precursor of a group of small lipids known as eicosanoids (139). Arachidonic acid is metabolized by two major enzyme pathways: (i) lipoxygenases, which catalyze the formation of hydroxyeicosatetraenoic acids, leading to the formation of leukotrienes; and (ii) cyclooxygenases 1 and 2, which catalyze the conversion of arachidonic acid into prostaglandins, prostacyclins and thromboxanes. Prostaglandins have 10 subclasses, of which D, E, F G, H and I are the most important (65). Inflamed gingiva synthesizes significantly larger amounts of prostaglandins when incubated with arachidonic acid than does healthy gingiva (167). Prostaglandin E_2 is a potent stimulator of alveolar bone resorption (41, 69). Within gingival lesions, prostaglandin E_2 is mainly localized to macrophage-like cells and is secreted when stimulated with bacterial lipopolysaccharide (148). Periodontal ligament cells also produce prostaglandin E_2, even when unstimulated. This secretion is enhanced by interleukin-1beta, tumor necrosis factor alpha and parathyroid hormone (196, 205, 206). It is important to note that prostaglandin E_2 has biphasic actions on immune function. In high doses, it decreases the levels of IgG, but at low doses it has the potential to increase IgG. When combined with interleukin-4, low doses of prostaglandin E_2 induce a synergistic rise in IgG production, suggesting an immune-regulatory role for prostaglandin E_2 (79).

Destruction of periodontal tissues

Destruction of bone

It is now generally accepted that disruption of the balance between osteoblast and osteoclast activities by bacterial products and inflammatory cytokines constitutes the main underlying causes of inflammation-induced bone loss (145). Lipopolysaccharide directly stimulates bone resorption when added to osteoclast precursor cultures containing osteoblasts and / or stromal cells (94). A toll-like receptor and inflammation-induced osteoclastogenesis pathway is implicated in the initiation of bone loss (187, 192). Inflammation-induced bone loss in response to periodontal infection has been well studied. Complex inflammatory signals and cytokine networks regulate osteoclastogenesis through RANKL, interleukin-1beta, interleukin-6, tumor necrosis factor alpha and prostaglandin E_2 (84) (Fig. 1).

Before the discovery of RANK, its ligand (RANKL) and its antagonist (osteoprotegerin), the development and the formation of osteoclasts were thought to be controlled by factors produced by osteoblasts and bone marrow stromal cells (162, 198). It is now clear that RANKL and osteoprotegerin are the key regulators of bone remodeling and are directly involved in the differentiation, activation and survival of osteoclasts and osteoclast precursors (2, 129, 261). RANKL is expressed by osteoblasts, stromal cells, chondrocytes and other mesenchymal cells. In addition, activated T-cells and B-cells can also express RANKL (111, 158, 235). RANK is expressed by osteoclast progenitors, mature osteoclasts, chondrocytes, monocytes / macrophages and dendritic cells (2, 91). The decoy receptor, osteoprotegerin, is known to be expressed by periodontal tissue cells, including fibroblasts and periodontal ligament cells (145). Blocking RANKL activity with osteoprotegerin significantly inhibits bone loss in rheumatoid arthritis, osteoporosis, cancer-related bone metastasis and diabetes-associated alveolar bone destruction (25, 87, 89, 122, 158, 169),

confirming the critical role of the RANKL / RANK / osteoprotegerin triad in osteoclastogenesis. However, it is not that simple. Macrophage colony-stimulating factor is also required, which is produced by osteoblasts / stromal cells (155, 230). The periodontal implication of the macrophage colony-stimulating factor requirement is that the pathogen, stress or pathology that influences the production of macrophage colony-stimulating factor via proinflammatory cytokines will have a significant influence on subsequent osteoclast activity. For example, toll-like receptor 2 activation in human gingival fibroblasts up-regulates the expression of macrophage colony-stimulating factor (27).

It is known that lipopolysaccharide from different pathogens stimulates bone resorption *in vitro* and in animal models, as in primary mouse calvarial osteoblasts. The activation of toll-like receptor 2 and toll-like receptor 6 by lipopolysaccharide causes enhanced expression of RANKL through a myeloid differentiation primary response protein (MyD88)-dependent mechanism (210). Also, osteoclasts and their precursors have been shown to express toll-like receptors, especially toll-like receptors 2, 4 and 9 (83, 86). Moreover, in mouse calvarial osteoblasts, expression of toll-like receptors 4 and 9 results in the activation of nuclear factor of kappa light polypeptide gene enhancer in B-cells and increased secretion of tumor necrosis factor alpha and macrophage colony-stimulating factor (268). Lipopolysaccharide-induced production of interleukin-1beta through toll-like-receptor pathways can up-regulate RANKL and can also inhibit the expression of osteoprotegerin by osteoblasts, resulting in osteoclast formation in a prostaglandin E_2-dependent manner (224). The crucial role of toll-like receptor 2 is that it substantially decreases the responses to lipopolysaccharide (27). These findings point out that lipopolysaccharide, directly via toll-like receptor pathways, induces osteoclast development and activity. Thus, it is believed that toll-like receptors influence the inflammatory response in the bone microenvironment and may play a critical role in modulating inflammation-induced osteoclastogenesis and bone loss. It is also interesting that recent evidence also points to important roles for resident cells in periodontal bone loss because periodontal ligament fibroblasts and osteoclast precursors synergistically increase the expression of genes related to osteoclastogenesis (20).

Destruction of extracellular matrix

There is significant evidence showing that collagenases, along with other matrix metalloproteinases, play an important role in periodontal tissue destruction. Matrix metalloproteinases are a family of structurally related, but genetically distinct, enzymes that degrade extracellular matrix and basement membrane components. This group of 23 human enzymes is classified into collagenases, gelatinases, stromelysins, membrane-type matrix metalloproteinases and other matrix metalloproteinases, mainly based on the substrate specificity and the molecular structure. Matrix metalloproteinases are involved in physiological processes such as tissue development, remodeling and wound healing. Matrix metalloproteinase activity is controlled by changes in the delicate balance between the expression and synthesis of matrix metalloproteinases and their major endogenous inhibitors, tissue inhibitor of matrix metalloproteinases. It is clear that matrix metalloproteinases are up-regulated in periodontal inflammation (241). Matrix metalloproteinase activation involves tissue and plasma proteinases and bacterial proteinases, together with oxidative stress (174, 242).

The expression and pathologic release of matrix metalloproteinases was originally thought to be limited to neutrophils (241), but it is now clear that a broad range of cell types present in normal and diseased human periodontium (including gingival epithelial cells, fibroblasts, endothelial cells, monocytes / macrophages and plasma cells) express distinct matrix metalloproteinases (77, 114, 234, 250).

Transcription of matrix metalloproteinase genes is very low in healthy periodontal tissue. In periodontal disease, secretion of specific matrix metalloproteinases is stimulated or down-regulated by various cytokines. The main stimulatory cytokines for matrix metalloproteinases are tumor necrosis factor alpha, interleukin-1 and interleukin-6. It is also known that active matrix metalloproteinases are capable of activating other matrix metalloproteinases in a mutual activation cascade (248). Certain cytokines are specifically related to particular matrix metalloproteinases. For example, interleukin-1beta and tumor necrosis factor alpha can stimulate the secretion of matrix metalloproteinases 3, 8 and 9 from gingival fibroblasts and the secretion of matrix metalloproteinase-13 from osteoblasts. Transforming growth factor beta suppresses the transcription of matrix metalloproteinase-1, -3 and -8 genes, but induces matrix metalloproteinase-2 and matrix metalloproteinase-13, mainly in keratinocytes (19, 106, 124).

The involvement of matrix metalloproteinases in inflammation is an active area of investigation. A good example of the interaction is interleukin-8 secretion in response to bacterial biofilm. Interleukin-8 recruits neutrophils to the site containing biofilm. The neutrophils will secrete cytokines, as well as matrix metalloproteinases 8 and 9 (221), resulting in the degradation of the extracellular matrix and the signaling other effector cells to produce matrix metalloproteinases. The major collagen-degrading enzyme in periodontitis is matrix metalloproteinase-8, which is mainly produced by neutrophils. This enzyme is found in gingival crevice fluid and saliva in diseased periodontal tissue. The main function of matrix metalloproteinase-8 is the degradation of interstitial collagens (221).

Matrix metalloproteinase-1 (collagenase-1) from mononuclear phagocytes, fibroblasts and epithelial cells has a wide range of substrates. It digests interstitial collagen, extracellular matrix components and soluble nonmatrix mediators (221). Matrix metalloproteinase-9 (gelatinase B) is a gelatinolytic enzyme that degrades several types of extracellular matrix, including basement membrane type IV collagen (135). Matrix metalloproteinase-9 is expressed by neutrophils, but also by cultured epithelial cells. The production of matrix metalloproteinase-9 is stimulated by several cytokines, especially tumor necrosis factor alpha, epidermal growth factor and by some bacterial products such as lipopolysaccharide and phospholipase C (54, 194).

Matrix metalloproteinase-2 (gelatinase A) has been shown to be strongly expressed in inflamed pocket epithelium and to be important in epithelial cell migration (159). Matrix metalloproteinase-13 (collagenase 3) is expressed by the basal cells of the gingival pocket epithelium (240); it degrades type I, type III and type IV collagens, as well as fibronectin, tenascin and some proteoglycans (105, 120). Matrix metalloproteinase-13 plays an important role in the growth of pocket epithelium into periodontal connective tissue. Some oral bacterial species, especially *Fusobacterium nucleatum*, induce matrix

metalloproteinase-13 (241). Matrix metalloproteinase-7 (matrilysin) is another epithelial matrix metalloproteinase with a broad spectrum of substrates. It degrades fibronectin, laminin, type IV collagen, gelatin, elastin, entactin, tenascin and proteoglycans. The enzyme is not commonly secreted by the gingival tissues and has not been reported in human gingival epithelium or in the pocket epithelium of periodontitis patients. It is expressed constitutively in many adult epithelial cells, most notably in the salivary glands, and its secretion is observed in suprabasal epithelial cells (203, 255). Some periodontal pathogens, including *F. nucleatum, Fusobacterium necrophorum, Porphyromonas endodontalis and Prevotella denticola*, were found to induce the expression of matrix metalloproteinase-7 in porcine gingival epithelial cells (241). Overall, the role of matrix metalloproteinase-7 in periodontal disease is not clear.

Matrix metalloproteinase-3 (stromelysin-1) does not digest interstitial collagen. The main substrates of matrix metalloproteinase-3 are basement membrane components such as laminins and type IV collagen. Matrix metalloproteinase-3 is found in gingival crevice fluid and gingival tissue during periodontal inflammation (47, 164, 248).

Regulation of matrix metalloproteinase activity is a function of tissue inhibitor of metalloproteinases. The tissue inhibitor of metalloproteinases class of enzymes function in the regulation of extracellular matrix metabolism. Four members of the family of tissue inhibitor of matrix metalloproteinases (tissue inhibitor of matrix metalloproteinases 1–4) have been identified to date. Although the main function of tissue inhibitor of matrix metalloproteinases is to inhibit matrix metalloproteinases, they also regulate matrix metalloproteinase transportation, stabilization and localization in the extracellular matrix. Tissue inhibitor of matrix metalloproteinases 1, 2 and 4 are secreted extracellular proteins, whereas tissue inhibitor of matrix metalloproteinase 3 is an extracellular matrix-bound molecule (248).

Resolution of inflammation

Periodontal inflammation begins as a protective response to bacterial biofilm. In susceptible individuals, periodontal inflammation fails to resolve and chronic inflammation becomes the periodontal pathology. Periodontal disease results from excess inflammation and may be considered a failure of resolution pathways. An essential goal of interventions in inflammatory disease is the return of tissue to homeostasis, defined as an absence of inflammation. Hence, the rapid and complete elimination of invading leukocytes from a lesion is the ideal outcome following an inflammatory event (243). Accordingly, inadequate resolution and failure to return tissue to homeostasis results in neutrophil-mediated destruction and chronic inflammation (245), with destruction of both extracellular matrix and bone, and scarring and fibrosis (244). Scarring and fibrosis in periodontitis prevent the return to homeostasis (243).

To date, the efforts to control inflammation have been focused on the use of pharmacologic agents that inhibit proinflammatory mediator pathways (e.g. nonsteroidal anti-inflammatory drugs) (214). Nonsteroidal anti-inflammatory drugs target cyclooxygenase 1- and cyclooxygenase 2-dependent pathways, inhibiting the generation of prostanoids. Newer

classes of inhibitors target lipoxygenase pathways and leukotriene production, or tumor necrosis factor alpha. The side-effect profiles of these agents prohibit their extended use in periodontal therapy.

More recent discoveries have uncovered the natural proresolving pathways, which are an extension of the same eicosanoid pathways that produce proinflammatory mediators. The physiologic end of the acute inflammatory phase occurs when there is a “class switch” of eicosanoid pathways in neutrophils (138, 243). This class switch is mediated by the up-regulation of 15-lipoxygenase by neutrophils late in inflammation. Neutrophils in the early acute phase produce only 5-lipoxygenase for the production of leukotrienes. 15-lipoxygenase catalyzes a second reaction with hydroxyeicosatetraenoic acid products generated earlier by neutrophils or other cells (213). The series of enzymatic reactions starts with the oxidation of arachidonic acid by a lipoxygenase (5-, 12-or 15-lipoxygenase, depending on the cell of origin). A 5-, 12- or 15-S-hydroxy-(p)-eicosatetraenoic acid intermediate is produced, which is then further acted on by 15-lipoxygenase to induce the synthesis of doubly substituted intermediates (5, 15 hydroxy-(p)-eicosatetraenoic acids, for example) that are further metabolized into lipoxins, such as lipoxins A_4 and B_4 (109, 245). Lipoxins are receptor agonists that stimulate the resolution of inflammation and promote the restoration of tissue homeostasis through a number of mechanisms. These include limiting the migration of polymorphonuclear neutrophils into sites of inflammation and modulating the phenotype of macrophages to stimulate the uptake of apoptotic polymorphonuclear neutrophils without secreting proinflammatory cytokines (156, 157, 217).

Unlike other nonsteroidal anti-inflammatory drugs, aspirin has unique characteristics. Aspirin acetylates cyclooxygenase 2 to inhibit further production of prostanoids from arachidonic acid metabolism, but the acetylated cyclooxygenase 2 has new enzyme activity as a 15-epi-lipoxygenase. This alternative pathway leads to the synthesis of 15-*R*-hydroxy-(p)-eicosatetraenoic acid. This molecule is transformed into 5(6)-epoxytetraene with the help of 5-lipoxygenase, and the product is 15-epi-LXs or aspirin-triggered lipoxins (245). Aspirin-triggered lipoxin, the epimer of native lipoxin, possesses more powerful proresolving properties (32, 218, 245).

Lipoxins are the natural proresolving molecules derived from endogenous fatty acids (arachidonic acid). Dietary fatty acids of the omega-3 class are also metabolized by similar pathways, and the products (resolvins and their aspirin-triggered derivatives) have similar biologic activity to lipoxins (215, 243). Resolvins stimulate the resolution of inflammation through multiple mechanisms, including preventing neutrophil penetration, the phagocytosis of apoptotic neutrophils to clear the lesion and enhancing the clearance of inflammation within the lesion to promote tissue regeneration (10, 81, 212). Interestingly, the classic inflammatory eicosanoids (i.e. prostaglandins and leukotrienes), in addition to activating and amplifying the cardinal signs of inflammation, are responsible for inducing the production of mediators that have both anti-inflammatory and proresolution activities, reinforcing the active nature of the resolution process (216). In an animal model of periodontitis, treatment with resolvin-E1 completely eliminated the signs of inflammation, enabling the regeneration of lost tissues (81).

Conclusion

Periodontal diseases are inflammatory diseases in which microbial etiologic factors induce a series of host responses that mediate inflammatory events (Fig. 1). In susceptible individuals, dysregulation of inflammatory and immune pathways leads to chronic inflammation, tissue destruction and disease. Physiologic inflammation is a well-orchestrated network of cells, mediators and tissues. It is very important to consider the inflammatory / immune response as a whole, rather than many different modules working separately. As disease appears to be the result of loss of regulation and a failure to return to homeostasis, it is important to achieve a more complete understanding of the molecular and cellular events in this complex system.

The paradigm shift in our understanding of inflammatory disease, such as periodontitis, is that resolution of inflammation is an active, rather than a passive, process that activates specific biochemical programs of resolution. Precursor fatty-acid substrates from cells (arachidonic acid) and dietary sources (omega-3 fatty acids) yield lipid mediators (lipoxins and resolvins, respectively) that counter-regulate proinflammatory signals. It is increasingly evident that future care of periodontal infections and periodontal surgical patients will rely on clinicians having a detailed map and molecular appreciation of the resolution programs for inflammation and tissue injury. Systematic temporal study of infection and resolution in human tissues is of paramount importance in the treatment of bacterially initiated disease. Studies of models of disease suggest that the shift to chronicity of the infection and the persistence of the pathogen results from increased inflammation and a failure of innate mucosal antibacterial systems. Susceptibility to chronic inflammatory disorders may therefore result from uncontrolled resolution of the inflammatory process. Considering the limited and semi-successful treatment options for periodontitis, research on the orchestration of this complex system can bring us one step closer for better treatment opportunities. As many current and widely used drugs have been developed without knowledge of their impact in resolution circuits, some agents, such as selective cyclooxygenase 2 inhibitors and certain lipoxygenase inhibitors, have proven to be toxic to the resolution programs (216). It will be important to learn whether resolution pharmacology leads to new treatments for human disease.

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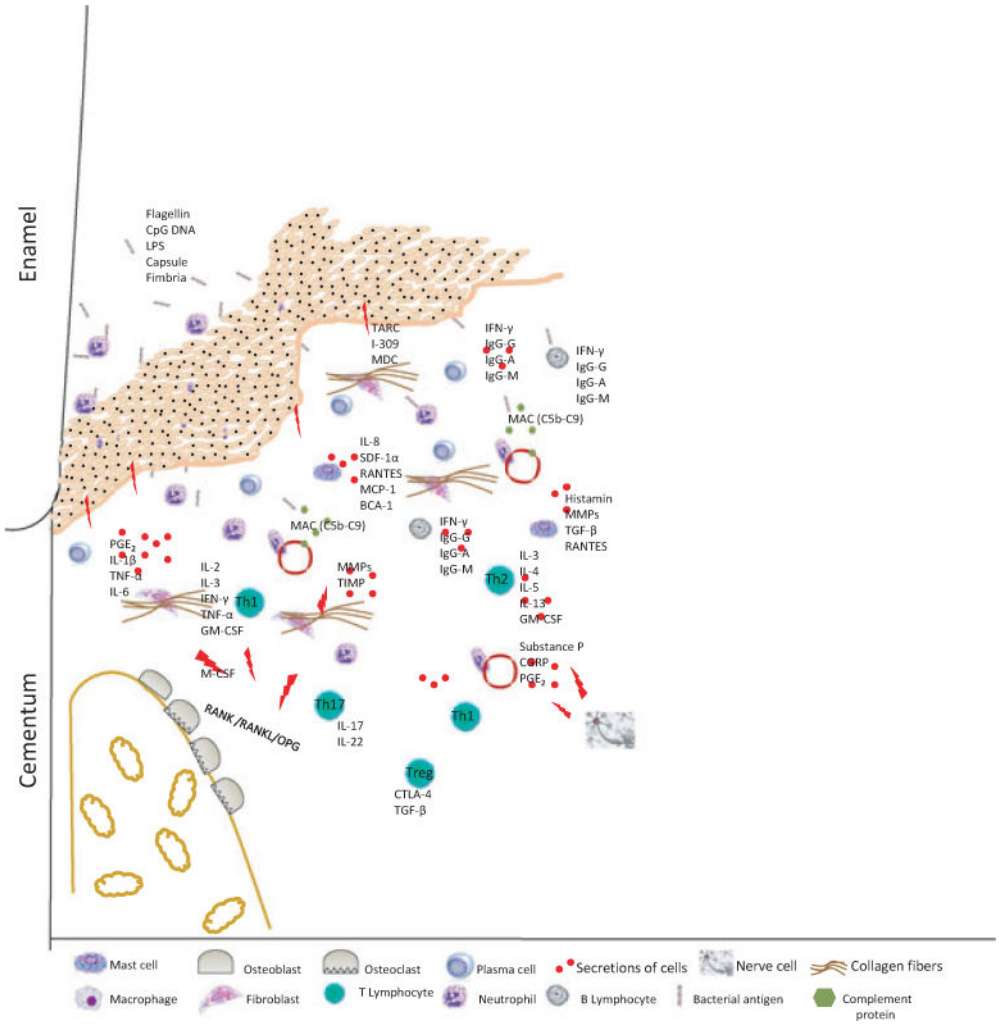

Fig. 1.

The immune inflammatory response in periodontitis is complex and involves both innate and acquired immunity. This diagram presents an overview of the effector molecules and effector cells in the pathogenesis of periodontitis based on our current understanding of disease pathways. BCA-1, B cell-attracting chemokine 1; CGRP, calcitonin gene-related peptide; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; GM-CSF, granulocyte–macrophage colony-stimulating factor; IFN-γ, interferon gamma; Ig-A, immunglobulin A; Ig-G, immunglobulin G; Ig-M, immunglobulin M; IL-1β, interleukin-1beta; IL-2, interleukin-2; IL-3, interleukin-3; IL-4, interleukin-4; IL-5, interleukin-5; IL-6, interleukin-6; IL-8, interleukin-8; IL- 13, interleukin-13; IL-17, interleukin-17; IL-22, interleukin-22; LPS, lipopolysaccharide; M-CSF, macrophage colony-stimulating factor; MAC, membrane attack complex; MCP-1, macrophage chemotactic protein-1; MDC, macrophage-derived chemokine; MMPs, matrix metalloproteinases; OPG, osteoprotegerin; PGE_2, prostaglandin E_2; RANTES, regulated and normal T cell expressed and secreted; SDF-1a, stromal cell-derived factor-1alpha; TARC, thymus and activation-regulated chemokine; TGF-β, transforming growth factor beta; Th1, T-helper 1 cell; Th2, T-helper 2

cell; Th17, T-helper 17 cell; TIMP, tissue inhibitor of matrix metalloproteinases; TNF-α, tumor necrosis factor alpha; Treg T-regulatory cell.

Table 1

The source cell, location and associated bacteria for toll-like receptors.

Receptor	Location	Cells	Bacteria
Toll-like receptor 1	Cell membrane	Myeloid dendritic cells, monocytes	Not specified
Toll-like receptor 2	Cell membrane	Monocytes, natural killer cells, myeloid dendritic cells,mast cells, T-cells, epithelial cells	*Porphyromonas gingivalis* *Escherichia coli* *Tannerella forsythia* *Prevotella intermedia* *Prevotella nigrescens* *Treponema denticola*
Toll-like receptor 3	Intracellular	Myeloid dendritic cells, natural killer cells, epithelial cells	Not specified
Toll-like receptor 4	Cell membrane	Monocytes, mast cells, neutrophils, T cells, epithelial cells, endothelial cells	*Aggregatibacter actinomycetemcomitans*, *Veillonella parvula*
Toll-like receptor 5	Cell membrane	Monocytes, natural killer cells, myeloid dendritic cells epithelial cells	Not specified
Toll-like receptor 6	Cell membrane	Myeloid cells, mast cells, B-cells, myeloid dendritic cells	*Escherichia coli*
Toll-like receptor 7	Intracellular	Plasmacytoid dendritic cells, B-cells, eosinophils	Not specified
Toll-like receptor 8	Intracellular	Natural killer cells, T-cells, myeloid cells, myeloid dendritic cells	Not specified
Toll-like receptor 9	Intracellular	Plasmacytoid dendritic cells, B-cells, natural killer cells	*Porphyromonas gingivalis* *Aggregatibacter actinomycetemcomitans*
Toll-like receptor 10	Cell membrane	B-cells, plasmacytoid dendritic cells, myeloid dendritic cells	Not specified
Toll-like receptor 11	Intracellular	Macrophages, dendritic cells, epithelial cells	Not specified

Table 2

Chemokine classification codes, designated names and affected cell types.

Receptor (classification code)	Cell type affected	Ligand (classification code)	Ligand (designated name)
CCR1	Monocytes/macrophages	CCL3	MIP-1α
	Neutrophils	CXCL8 CXCL6 CXCL1 CCL23	IL-8 GCP-2 GROα CKβ8
	Osteoclast precursors and mature osteoclasts	CCL5 CCL7 CCL9	RANTES MCP-3 MIP-1γ
CCR2	Monocytes/macrophages and osteoclast precursors	CCL2	MCP-1
CCR3	Th1 lymphocytes	CXCL9	MIG
	Th2 lymphocytes and osteoblasts	CXCL10 CXCL11 CCL7 CCL11 CCL13 CCL15	IP-10 I-TAC MCP-3 Eotaxin MCP-4 HCC-2
CCR4	Th2 lymphocytes and osteoblasts	CCL22 CCL17 CXCL12	MDC TARC SDF-1
CCR5	Monocytes/macrophages, Th1 lymphocytes and osteoblasts	CCL5	RANTES
	B lymphocytes	CXCL13	BCA-1
CCR8	Th2 lymphocytes	CCL1	I-309
CXCR1	Osteoclast precursors and osteoblasts	CXCL8	IL-8
CXCR3	Osteoclast precursors and Osteoblasts	CXCL9	MIG
CXCR4	Osteoclast precursors, mature osteoclasts and osteoblasts	CXCL12	SDF-1
CXCR5	Osteoblasts	CCL5 CXCL13	RANTES BCA-1

BCA-1, B cell-attracting chemokine 1; CCL, chemokine (C-C motif) ligand; CCR, chemokine (C-C motif) receptor; CKb8, transcript variant CKb8; CXCL, chemokine (C-X-C motif) ligand; CXCR, chemokine (C-X-C motif) receptor; GCP-2, granulocyte chemotactic protein 2; GROa, melanoma growth stimulatory factor; HCC-2, hemofiltrate CC-chemokine-2; IL-8, interleukin-8; I-TAC, interferon-inducible T-cell chemoattractant; MCP-3, macrophage chemotactic protein-3; MCP-4, macrophage chemotactic protein-4; MDC, macrophage-derived chemokine; MIG, monokine induced by gamma interferon; MIP-1a, macrophage inflammatory protein 1alpha; MIP-1c, macrophage inflammatory protein 1gamma; RANTES, regulated and normal T cell expressed and secreted; SDF-1, stromal cell-derived factor-1; TARC, thymus and activation-regulated chemokine; Th1, T-helper 1; Th2, T-helper 2.