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Mast cells – a role in periodontal diseases?

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Abstract

Objectives: Limited attention has been given to the role mast cells may play in periodontal diseases.

Background: Mast cells are indeed found abundantly below and within several types of mucosal epithelia. On the basis of their proteinase content, mast cells are divided into connective tissue (CT) and mucosal phenotypes. The CT phenotype contains both tryptase and chymase (MC^{TC}), while the mucosal phenotype contains only tryptase (MC^{T}). The in vivo significance of different mast cell phenotypes has not yet been fully established. Mast cells are able to phagocytose, process and present antigens as effectively as macrophages.

Results: Recently mast cells were found in high numbers in chronically inflamed gingival tissue taken from patients with chronic marginal periodontitis (CMP). The number of mast cells was found to be even higher in HIV^{+} patients with CMP. Furthermore, mast cells also express strongly matrix metalloproteinases (MMPs), which are key enzymes in degradation of gingival extracellular matrix. Mast cells may release preformed cytokines directing local innate and adaptive immune responses. The present review will focus on possible roles for mast cells in periodontal diseases.

Conclusions: We certainly feel that this is a key cell in inflamed periodontal tissue and its role in periodontitis needs to be revisited.

Key words: extracellular matrix; immune responses; inflammation; mast cells; periodontitis

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Periodontal Inflammation

Gingival inflammation and periodontal diseases are triggered by accumulation of bacteria at the dentogingival margin. The host generates an inflammatory cell infiltrate in the tissue subjacent to the periodontal pocket as a defense against the microbial threat. The infiltrate consists primarily of leukocytes including plasma cells, lymphocytes, macrophages and neutrophils that serve several functions in the defense against periodontal infection (Page & Schroeder 1976). Important functions of neutrophils are phagocytosis and killing of microorganisms – critical factors in minimizing the destructive effects of the periodontopathogenic bacteria (Dennison & Van Dyke 2000). While macrophages also operate as phagocytes, the cells may as well present antigens to T cells and amplify specific immune responses. Fcγ-receptors (FcγRs) expressed on phagocytes play crucial roles in antibody-mediated phagocytosis (Van den Herik-Oudijk et al. 1995, Raghavan & Bjorkman 1996). Lymphocytes, neutrophils and macrophages can secrete a range of biologically active molecules such as cytokines and proteases with potential profound effects on structural proteins (Lee et al. 1995, Okamoto et al. 1997).

We have examined several properties of the inflammatory cell infiltrate in chronic periodontitis (Odden et al. 1995, Myint et al. 1999, Steinsvoll et al. 1999, Myint et al. 2000), and interestingly, we found high numbers of mast cells equal to and often surmounting the numbers of macrophages in the inflamed periodontal lesion (Myint et al. 2002). Many reports have, during the last 15 years, shed new light on the mast cell as pivotal cell in both innate and acquired immunity (Echtenacher et al. 1996, Malaviya et al. 1996, Abraham & Malaviya 2000), and in wound-healing processes (Steinsvoll et al. 1999, Berton et al. 2000, Huttunen et al. 2000). Recently, we found that mast cells strongly express matrix metalloproteinase (MMP)-1, -2 and -8 (Næsse et al. 2003), which are key enzymes in degradation of periodontal soft tissue.

In the present review, we suggest mast cells as key players in gingival homeostasis that may be important in the progression of periodontitis. It is our opinion that this abundant, pleiotropic and potent cell type needs to be revisited.

Mast Cell Origin

Mast cells originate from pluripotential hematopoietic cells in the bone marrow, undergo part of their differentiation in this site, then enter the circulation and

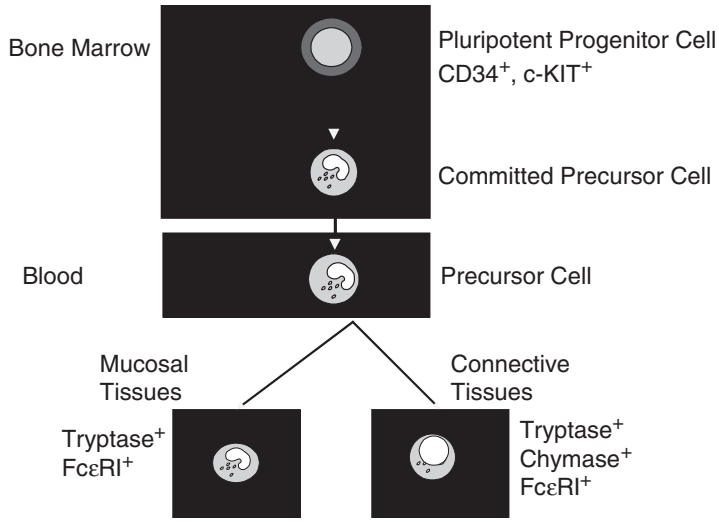

Fig. 1. Mast cells originate from pluripotential hematopoietic cells in the bone marrow, undergo part of their differentiation in this site, then enter the circulation and complete their differentiation in peripheral mucosal or connective tissue microenvironments.

complete their differentiation in peripheral mucosal or connective tissue (CT) microenvironments rich in fibroblasts and other mesenchymal elements (Arock et al. 1994, Fodinger et al. 1994, Metcalfe et al. 1995) (Fig. 1). One hallmark in mast cell development is that c-kit (CD117), the receptor of stem cell factor (SCF), is expressed by mast cells and their progenitors, including the pluripotential progenitors of mast cells, committed mast cell progenitors, immature mast cells and mature tissue mast cells. SCF promotes the proliferation of mast cell progenitors, immature or mature mast cells, stimulates the maturation of mast cell precursors or immature mast cells, and alters mast cell phenotype and mediator contents (Galli & Kitamura 1987, Kanakura et al. 1988, Galli & Hammel 1994, Kitamura et al. 2000).

Mast Cell Heterogenity

On the basis of their proteinase content, MCs are divided into CT and mucosal phenotypes (Fig. 1). The CT phenotype contains both tryptase and chymase (MC^{TC}), while the mucosal phenotype contains only tryptase (MC^{T}) (Irani et al. 1989) (Fig. 2a). The in vivo significance of different mast cell phenotypes has not yet been fully established. Mast cells are able to phagocytose, process and present antigens as effectively as macrophages (Echtenacher et al. 1996, Malaviya et al. 1996, Dines & Powell, 1997, Abraham & Arock 1998, Abraham & Malaviya 2000, Henz et al. 2001) (Fig. 3).

Mucosal Mast Cells

Mast cells play important roles in mucosal inflammation, host defense and tissue repair. When triggered by locally produced cytokines or bacterial products (e.g. lipopolysaccharides), the cells can release large quantities of pre-stored mediators such as histamine, leukotrienes, platelet-activating factor (PAF), proteases and tumor necrosis factor-α (TNF-α) (Befus et al. 1987, 1988, Lin & Befus 1999, Befus et al. 1999a, b). Mast cells are abundant below and within mucosal epithelia. In intestinal lamina propria, there are normally about 20,000 cells/mm^3, but cell numbers increase upon intestinal parasitic infections and inflammatory bowel diseases (Lin & Befus 1999). Limited attention has been given to the role mast cells may play in periodontal diseases (Zachrisson & Schultz-Haudt 1968). Mast cells are seen scattered throughout gingival CT, often in close association with endothelial cells, but are also found sub- and intra-epithelially (Lin & Befus 1999, Steinsvoll et al. 1999). In inflamed and in healing gingiva, numbers of mast cells have been found to be increased (Gunhan et al. 1991, Kennett et al. 1997, Steinsvoll et al. 1999).

Mast Cell Mediators

Histamine

Histamine is a well-known mast cell mediator that is synthesized in the Golgi apparatus by decarboxylation of histidine and stored in granules at 100 mM concentration. Once released, methylation and oxidation rapidly catabolize histamine. The broad distribution of histamine H_1, H_2 and H_3 receptors bestow histamine with wide-ranging biological effects.

Lipid-derived mediators

Lipid-derived mediators from mast cells can be divided into two classes, AA (arachidonic acid) metabolites and the 2-acetylated phospholipids structurally related to PAF. In mast cells, FcεRI cross-linking induces transient phosphorylation of cytosolic phospholipase A_2 ($cPLA_2$) in parallel with the AA release and subsequently increases $cPLA_2$ expression that enables the cells to respond to a secondary stimuli and release more AA (Murakami et al. 1995). The released free AA is further metabolized by COX (cyklooxygenase) and LO (lipooxygenase) to release prostaglandins (PG), thromboxanes (TX), leukotrienes (LT) and 5-, 12-HETEs (hydroxy-eicosatetraenoic acids). In human mast cells, PGD_2 (50–100 ng/10^6 cells) is the most abundant COX product and has a short half-life in the circulation. Mast cell-derived PGD_2 may participate in the development of airway hyperresponsiveness (Schwartz & Huff 1993). Human mast cells also produce LTC_4 in excess of LTB_4, and both have profound effects in inflammation. Mast cells also produce a series of free radicals including nitrogen radicals (NO) and oxygen radicals (superoxide anion, hydrogen peroxide and hydroxyl radical) (Schwartz & Huff 1993).

Proteoglycans

Proteoglycans are composed of a single-chain protein covalently linked with multiple glycosaminoglycan side chains. Two proteoglycans, heparin (3–8 pg/cell) and chondroitin sulfate E are found in human MC^{TC} and MC^{T}. Proteoglycans function as storage matrices for other preformed mediators, which might otherwise have deleterious effects on the mast cells themselves. Proteoglycans bind to histamine, neutral proteinases and acid hydrolases at acidic pH inside mast cell granules and appear to facilitate uptake, packaging and regulation of preformed mediators. Moreover, proteoglycans function as extracellular mediators, such as anticoagulant and anticomplementary effects and modulate neutral proteinases, which may have profound pathophysiological

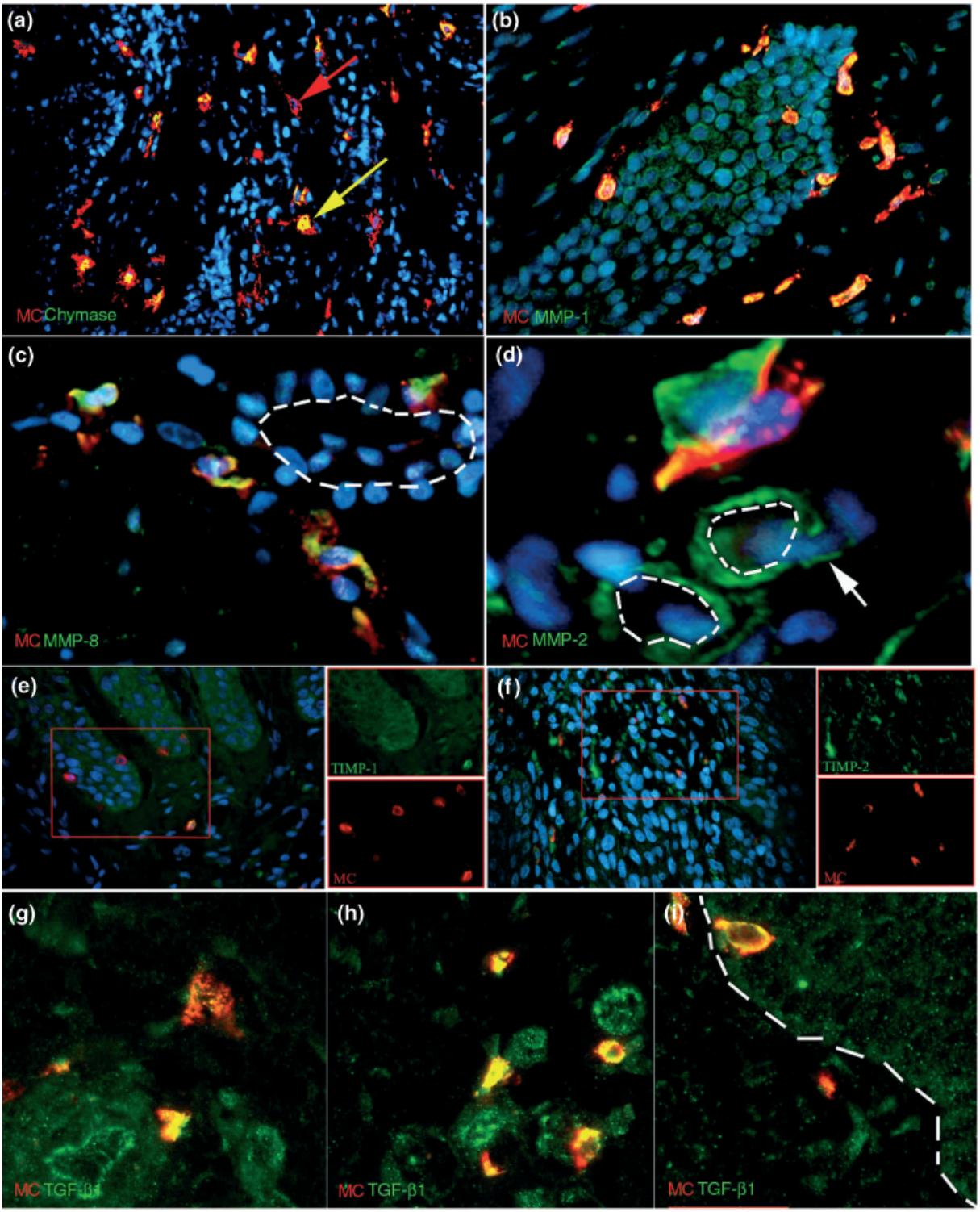

Fig. 2. The microphotograph shows double staining of mast cell tryptase combined with chymase (a), with matrix metalloproteinase (MMP)-1 (b), with MMP-8 (c), with MMP-2 (d), tissue inhibitors of metalloproteinase (TIMP)-1 (e), TIMP-2 (f) and TGF-β_1 (g–i). Tryptase-positive cells appear red while chymase, MMP-, TIMP- and TGF-β_1-positive cells are green, overlapping colors (double-stained) appear in yellow. The yellow arrow points to a connective tissue type mast cell containing both proteases whereas the red arrow indicates a mucosal mast cell containing only tryptase (a), and the white arrow depicts an MMP-2-positive cell that extravasates (d). The dashed line refers to blood vessels (c, d) and the basal cell layer of the epithelium (i). Blue color is nuclear staining with DAPI. Original magnification $\times$ 40.

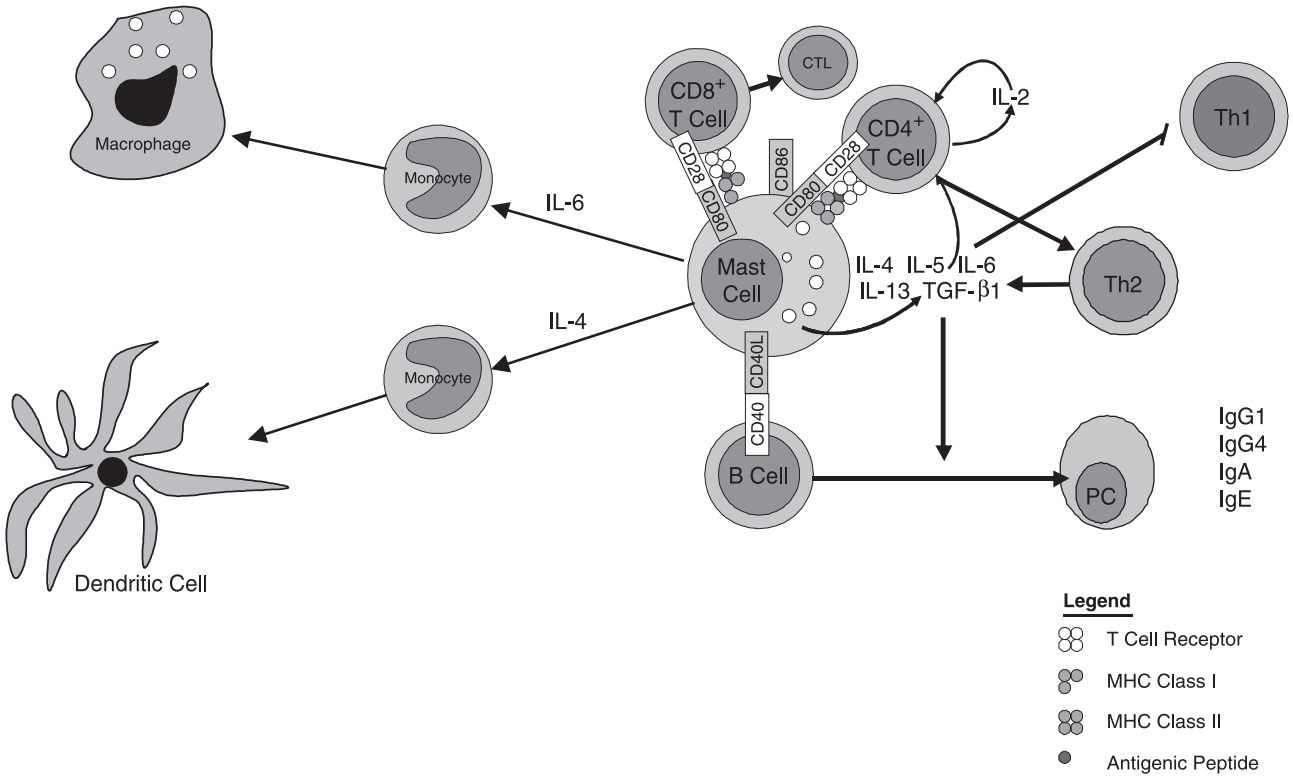

Fig. 3. Mast cells can phagocytize diverse particles, take up antigens and express a number of receptors, particularly MHC class I and II antigens, ICAM-1 and -3, CD43, CD80, CD86 and CD40L, which allow them to interact with T and B lymphocytes. They can also secrete numerous cytokines that induce and enhance recruitment and functions of lymphocytes. Mast cells can also activate B cells directly to produce IgE, but this activity and the ability to produce IL-4 or IL-13 is restricted primarily to basophil leukocytes and mucosal mast cells. Finally, recent evidence attributes a pivotal role to the cells in natural immunity to bacteria, and in the local differentiation of monocytes into macrophages and dendritic cells.

significance (Schwartz & Huff 1993, Boushey 1998, Dahlen et al. 1999, Cho 2000).

Mast cell cytokines

In humans a broad spectrum of cytokine protein and/or mRNA has been identified in mast cell lines or in vivo-derived mast cells, including SCF, TGF-β_1, TNF-α, bFGF, IL-1β, IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, MIP-1α, MIP-1β, RANTES, I-309 and MCP-1 (Lin & Befus 1999).

TNF-α is one of the best-described cytokines from different mast cell populations including in vivo-derived mast cells and mast cell lines from humans and rodents. In vivo-derived mast cells constitutively synthesize and release a substantial amount of TNF-α without obvious stimulation. By contrast, macrophages, T and B cells contain little or no preformed TNF-α bioactivity without stimulation. TNF-α production by mast cells can be up-regulated by ligation of FcεRI or FcγRIII, substance P, calcium ionophore and PMA, and down-regulated by IFN-α/β, IFN-γ, TGF-β_1, IL-10, prostaglandins (PGE_1, PGE_2 and misoprostol), β_2 adrenergic receptor agonists (salbutamol, salmeterol and isoproterenol), and various antiallergic drugs such as cyklosporin A, FK506, dexamethasone, sulfasalazine, sodium cromoglycate and nedocromil sodium (Lin & Befus 1999). Although TNF-α can be produced by an array of cells such as monocyte/macrophages, neutrophils, eosinophils and many others, the importance of mast cell-derived TNF-α in inflammation and host defense was elegantly illustrated using mast cell-deficient W/W^v mice in an acute peritonitis model (Echtenacher et al. 1996, Malaviya et al. 1996).

TGF-β_1 is a potent chemoattractant for leukocytes including neutrophils, monocytes and mast cells (Wahl 1991, Wahl et al. 1991, 1993) and is probably an important factor involved in formation of the inflammatory cell infiltrate, especially in chronic inflammatory lesions such as periodontitis. Many cell types in chronically inflamed periodontal tissue express TGF-β_1, including about 50% of the gingival mast cells (Steinsvoll et al. 1999) (Fig. 2g,h). Perivascular TGF-β_1^+ mast cells could be a contributing factor in the recruitment of inflammatory cells and act as local vascular gatekeepers. Interestingly, treatment of rat peritoneal mast cells with anti-TGF-β_1 antibody enhanced TNF-α-dependent cytotoxicity by 16% (Bissonnette et al. 1997), suggesting an autocrine effect of TGF-β_1 in the regulation of mast cell function.

IL-4 derived from mast cells at sites of inflammation may play a role in T-cell differentiation toward a T_H2 phenotype. Mast cells may present antigen to T cells as they express MHCII molecules, and the co-stimulatory molecules ICAM-1/3, CD80 and CD86 (Henz et al. 2001) (Fig. 3). Thus, mast cells are involved in the regulation of immune responses. Furthermore, since mast cells also can express CD40 ligand, it is possible these cells are able to promote immunoglobulin class switching to antibody isotypes supported by the T_H2 phenotype (Gauchat et al. 1993) (Fig. 3). A recent paper demonstrates mast cell-derived IL-4 as a dendritic cell differentiating factor from monocytes while IL-6 is crucial for

development into macrophages (Chomarat et al. 2000) (Fig. 3).

The content of cytokines may vary in distinct mast cell populations and be, at least in part, responsible for the functional heterogeneity of human mast cells. Bradding et al. (1995a, b) demonstrated in human bronchial biopsies that IL-5, IL-6 and TNF-α were expressed largely by MC^T, whereas IL-4 was present in both MC^T and MC^{TC}.

Mast cell serine proteinases

Mast cells contain an array of molecules with the potential to mediate breakdown of extracellular matrix. Tryptase and chymase are serine proteinases; tryptase may cleave fibrinogen, activate latent collagenase (Gruber et al. 1989), MMP-2 (Lohi et al. 1992), MMP-3 (Gruber et al. 1989), kininogens (Walls et al. 1992), hydrolyze neuropeptides, cause mucus secretion and be mitogenic for fibroblasts (Caughey 1991). Mast cell-derived tryptase is a potent chemoattractant for neutrophils (He et al. 1997), stimulates epithelial cell proliferation, secretion of IL-8 and increases epithelial expression of intercellular adhesion molecule-1 (Cairns & Walls 1996). Further, tryptase induces expression of mRNA for IL-1β and IL-8 in endothelial cells (Compton et al. 1998, 2000). Additionally, tryptase may stimulate peripheral sensory nerves to secrete inflammatory neuropeptides such as calcitonin gene-related peptide inducing neurogenic inflammation (Steinhoff et al. 2000). Chymase may degrade basal membranes and neuropeptides, activate latent IL-1β (Mizutani et al. 1991) or MMP-9 (Fang et al. 1997). The biological significance of these proteases in periodontitis remains to be solved. In a recent study, however, we only observed trace amounts of tryptase and chymase in the matrix extracellularly (Myint et al. 2002, Næsse et al. 2003). The presence of only small quantities of these proteases in the extracellular environment might indicate that the periodontal lesions were stable and quiescent without any substantial mast cell degranulation taking place, which was in accordance with the clinical appearance of the biopsy sites that displayed no signs of acute inflammation or suppuration.

Mast cell MMPs

MMPs play important roles in cell migration, wound healing and tissue remodeling, and have pathogenic roles in arthritis, periodontitis, glomerulonephritis, atherosclerosis and cancer cell invasion (Birkedal-Hansen et al. 1993, van der Zee et al. 1996, Nagase 1997, Parsons et al. 1997, 1998, McCawley & Matrisian 2000). MMPs are secreted in latent, inactive pro-enzyme forms, with plasmin and other MMPs as likely activators (Birkedal-Hansen et al. 1993, Nagase 1997, Parsons et al. 1997). MMP activity is further modulated by the tissue inhibitors of metalloproteinases (TIMP-1, -2 and -3), which partly control and stabilize MMPs (Matrisian et al. 1992, Birkedal-Hansen et al. 1993, Nagase 1997). In normal, steady-state tissues, only low levels of MMP activity are detected because MMPs are also tightly regulated on the transcription and secretion level (Nagase 1997). In a recent study, Næsse et al. (2003) found that gingival mast cells were the foremost producers of MMP-1, which is consistent with a report by Di Girolamo & Wakefield (2000). Mast cells strongly expressed both MMP-1 and -8, while about half expressed MMP-2 and TIMP-1. Only few cells expressed TIMP-2 (Næsse et al. 2003) (Fig. 2b–f). The observations rank mast cells among key cells in the pathogenesis of periodontitis: MMPs can be released and cause rapid extracellular matrix degradation and periodontal tissue destruction.

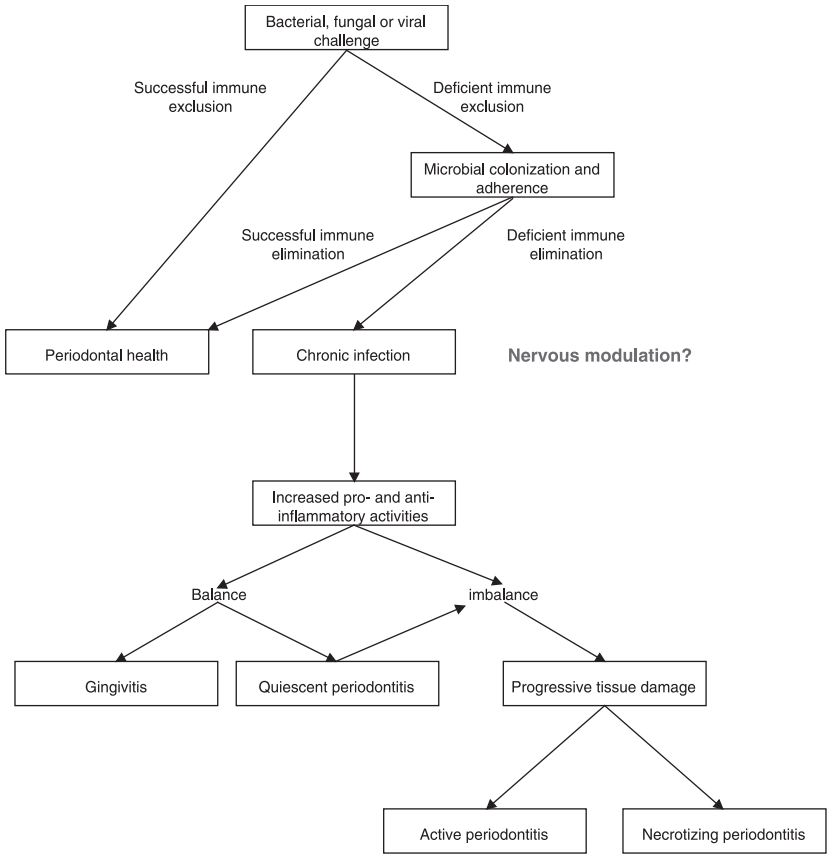

Fig. 4. Potential outcomes of gingival and periodontal infection. Mast cells operate at all levels in the figure. They are important in the first line of defense against infection, the host tries to prevent microorganisms to colonize the tissue (epithelial barriers with mast cells residing intra- and sub-epithelially, antibacterial substances in saliva). If immune exclusion is unsuccessful, microbes or their products may penetrate or invade gingival and periodontal tissues. This will induce immune elimination systems (phagocytosis, complement activation, generation of specific immune processes mediated by B and T cells). If the invading agents are cleared away, the tissue will become healthy again. If clearance fails, chronic infection of the gingival or periodontal tissue ensues. This is a balanced (but dynamic) condition where the infection is restrained physically (encapsulation) and functionally (phagocytosis and bacterial cell lysis). Pro- and anti-inflammatory agents are kept in balance and the disease remains non-progressive (gingivitis or quiescent periodontitis). Periodically, however, the balance may be disturbed, either by increasing strength of the attack or diminished defense by the host, and progressive loss of gingival and periodontal tissue may occur (active or necrotizing periodontitis).

Conclusion

Fig. 4 shows potential outcomes of gingival and periodontal infection where mast cells operate on all levels. Mast cells are important in the first line of defense against infection, the host tries to prevent microorganisms to colonize the tissue (epithelial barriers with mast cells residing intra- and sub-epithelially, and antibacterial substances in saliva). If immune exclusion is unsuccessful, microbes or their products may penetrate or invade gingival and periodontal tissues. This will induce immune elimination systems (phagocytosis, complement activation, generation of specific immune processes mediated by B and T cells where mast cells might have immune-regulatory functions) (Fig. 3). If the invading agents are cleared away, the tissue will become healthy again. If clearance fails, chronic infection of the gingival or periodontal tissue ensues. This is a balanced (but dynamic) condition where the infection is restrained physically (encapsulation) and functionally (phagocytosis and bacterial cell lysis). Pro- and anti-inflammatory agents are kept in balance and the disease remains non-progressive (gingivitis or quiescent periodontitis). Periodically, however, the balance may be disturbed, either by increasing strength of the attack or diminished defense by the host, and progressive loss of gingival and periodontal tissue may occur (active or necrotizing periodontitis) (Fig. 4). In all these processes mast cells play a pivotal role including wound healing. However, mast cells may also play a pathological role in other mucosal diseases such as oral lichenoid reactions, recurrent oral ulcerations and inflammatory bowel diseases, because these diseases are characterized by tissue breakdown that can be associated with MMP activity. The close association between peripheral nerves and mast cells needs further investigation to disclose a possible pathological interaction in these diseases. Mucosal mast cells together with T cells and other cells constitute a network that can orchestrate protective immunity or harmful inflammation, processes known to be modulated by the nervous system.

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