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Chapter

Immune Response in Gingival Disease: Role of Macrophage Migration Inhibitory Factor

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Abstract

The term periodontal disease encompasses a wide variety of chronic inflammatory conditions of the periodontium, including gingivitis and periodontitis. The gingival disease is an infectious process, which occurs due to the progression of untreated gingivitis. It is characterized by a destructive inflammatory process that affects the supporting tissues of the teeth, which causes the loss of the dental organs. As a result of inflammation, a wide range of cytokines and inflammatory mediators together contribute to tissue degradation and bone resorption. However, some molecules that have not been studied in the inflammatory process of this disease, such as the macrophage migration inhibitory factor (MIF) which is considered an important cytokine of the innate immune system; it is expressed constitutively in immune and nonimmune cells, and it is released immediately against bacterial stimuli, hypoxia, and proliferative signals. MIF has been described in some chronic degenerative, inflammatory, and autoimmune diseases. Previous studies have described that in murine models of periodontitis, MIF promotes the activation and differentiation of osteoclasts that could position this cytokine in the immunopathogenesis of gingival disease in humans.

Keywords: macrophage migration inhibitory factor, cytokine, gingival disease, periodontitis, osteoclastogenesis

1. Introduction

The periodontium is considered an organ constituted by a group of hard tissues (alveolar bone and cement) and soft tissues (periodontal ligament and gingiva). These tissues support the dental organs for a proper function in the oral cavity [1].

The gingiva is a specific oral, physical barrier (**Figure 1**) [2], which is a dynamic environment and continuously stimulated by the microbial imbalance, where

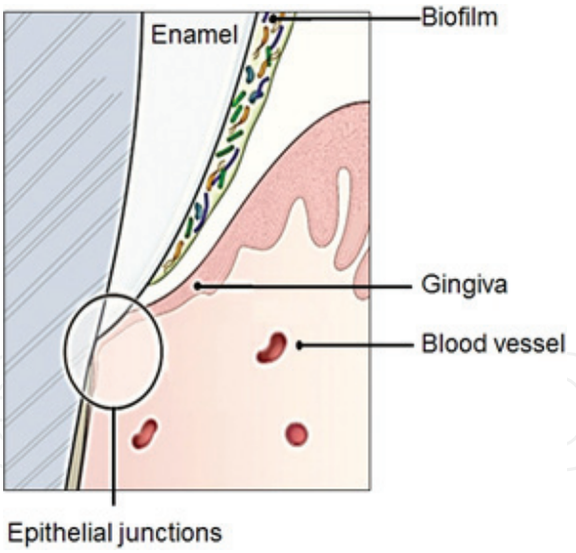

Figure 1.
Gingiva. The epithelial junction is a specific oral physical barrier.

homeostasis is frequently altered, which leads to that entails to an inflammatory event at the site [3].

Inflammatory cytokines and immune and nonimmune cells play, in the periodontium, an important defensive role in the gingival barrier [4]. However, the intimate relation between the epithelial junctions and the surface of the tooth can be interrupted by routine actions such as chewing and brushing and the formation of the biofilm, which can cause bacterial translocation [5].

2. Gingiva disease

The interaction between the gingival epithelial cells and the main pathogens (*Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans*, and *Tannerella forsythia*) [6] (**Figure 1**) is one of the first events that start with immunological response at the site, orchestrated by pro-inflammatory mediators as cytokines that can lead to gingival disease [3].

The gingival disease is defined as an inflammatory disorder initiated on the surface of the soft tissues, where the persistent inflammation can promote the destruction of the periodontium [7].

The disease occurs by a complex interaction between the microbial environment and the immune response of the host, which results in altered bone metabolism and connective tissue destruction [8]. It has been proposed that periodontopathogens are necessary but insufficient to promote the destruction of tissues and develop periodontal lesions because most of the damage is caused by the subversion of the host immune response [6].

2.1 Immune response in the gingiva

The adhesion and colonization by periodontopathogens in the gingiva trigger inflammatory through the liberation of endotoxins and bacterial products from the bacteria [9] which are recognized by the pattern recognition receptor (Toll-like receptors, cytoplasmic nucleotide oligomerization domain-like, lipopolysaccharide-binding protein, CD14) expressed in resident cells of the gingiva such as epithelial cells, fibroblasts, macrophages, neutrophils, and dendritic cells [10].

The subsequent signal translation activates signaling pathways that promote the expression of pro-inflammatory cytokines and chemokines [11].

Chemokine, cytokines, and inflammatory mediators such as leukotrienes increase vascular permeability and the expression of adhesion molecules that stimulate the infiltration of non-resident cells to the tissues such as neutrophils, macrophages, and lymphocytes [6]. Therefore, an inflammatory environment is initiated locally that includes prostaglandins, matrix metalloproteases, complement proteins, and cytokines [12].

Inflammation is continued by macrophages that increase the concentration of tumor necrosis factor alpha (TNF-α) and interleukin 1, 6 (IL-1, IL-6); at this moment more neutrophils are recruited in the furrow to try to control the infection [3, 11]. If the bacterial infection is not resolved by the inflammation, the antigens are captured, processed, and shown by antigen-presenting cells that activate naïve CD4 T lymphocytes at the subtype Th17 [13]. The profile of Th17 lymphocytes present in the gingival sulcus secretes cytokines such as IL-17 and IL-22 that enhance inflammation to eliminate extracellular bacteria [11].

The pro-inflammatory microenvironment could compromise the integrity of the alveolar bone that supports the dental organs which are maintained by the balance between the reabsorption of the old bone by the osteoclasts and the formation of the new bone by the osteoblasts; however, in periodontitis (PE), the cycle of bone remodeling is altered in favor of the resorption [14]. Key effectors in the microenvironment of bone resorption involve the molecule triad, receptor activator of nuclear factor-kappa B ligand (RANKL), receptor activator of nuclear factor-kappa B (RANK), and decoy receptor osteoprotegerin (OPG) [15, 16]. RANKL, which is produced by osteoblasts, stromal cells, T cells, and other sources, activates RANK on the surface of osteoclasts and osteoclast precursors [16]. The process of

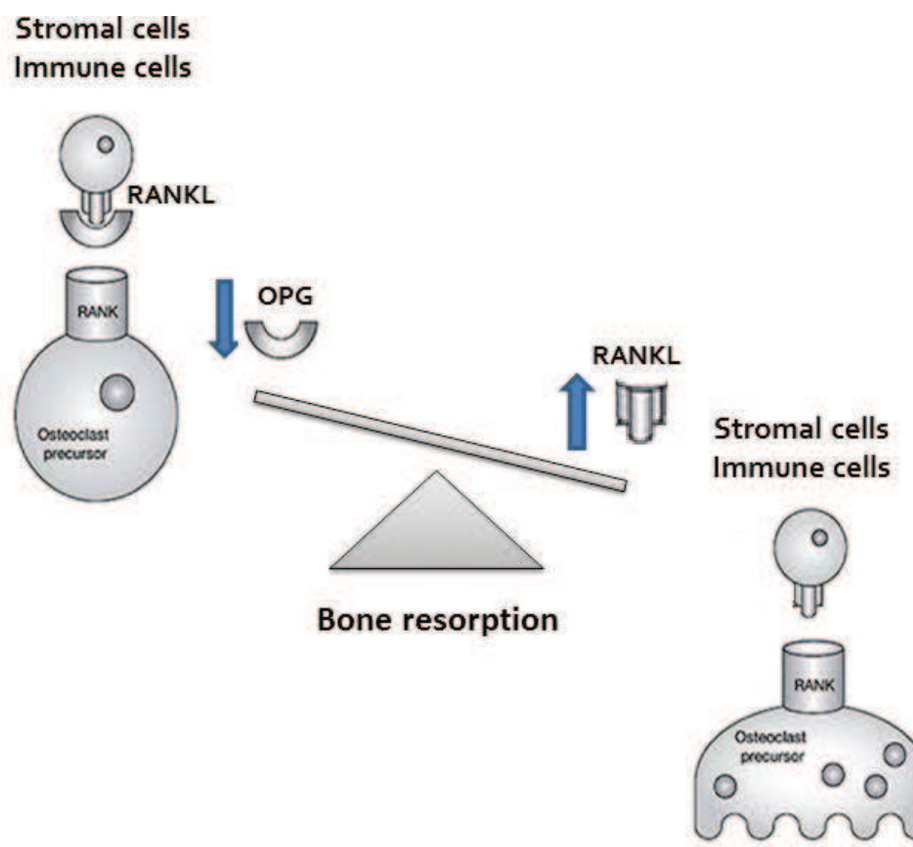

Figure 2.
Bone resorption. The osteoclast activity is regulated by the expression and interaction of RANK-RANKL-OPG [17]. Periodontal disease increased the resorption bone.

osteoclastogenesis begins by the binding of RANK-RANKL and can be interrupted by OPG that functions as a decoy receptor that blocks the binding of RANKL to RANK (**Figure 2**) [17].

The pro-inflammatory cytokines are proteins that have a principal role in the control, direction, amplitude, and duration of the immune response. They allow contact within the immune system and communication with other organs and tissue systems [8]. Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine; MIF is an important mediator of the innate immune response [18]; however, there are a few studies that describe its participation in PE, for its characteristics it can lead the environment of the inflammatory response in the disease.

3. Macrophage migration inhibitory factor (MIF)

MIF is a multifunctional protein, constitutively expressed in a wide variety of immune and nonimmune cells, such as eosinophils, neutrophils, granulocytes, monocytes/macrophages, B and T lymphocytes; endocrine; endothelial; epithelial; and neuronal cells [19].

MIF is a monomer of 115 amino acids forming a homotrimer; each has two antiparallel alpha helices that pack against a four-stranded beta-sheet. Each of the three monomers is arranged to form a barrel containing a channel that runs through the center of the protein along a molecule (**Figure 3**) [20].

MIF is stored in pre-formed and released rapidly in response to the stimulation from microbial products (LPS), proliferative signals, and hypoxia [18–20], works in a paracrine and autocrine form, promotes the activation of cells, as well as the release of pro-inflammatory cytokines, and counteracts the effects of glucocorticoids at the sites of inflammation [18].

MIF activates in macrophages functions such as phagocytosis, adherence, motility and transendothelial migration [19].

Monocytes/macrophages store large amounts of preformed MIF that are released against stimulation with LPS, glucocorticoids, Gram-positive exotoxins, cytokines, and pro-inflammatory mediators, which have an important role in the local secretion of MIF during the innate immune response [19, 21].

3.1 MIF and inflammation

The physiological role of MIF is to counteract the inhibitory effects of steroids on the inflammatory and immune response; MIF is a pro-inflammatory cytokine that

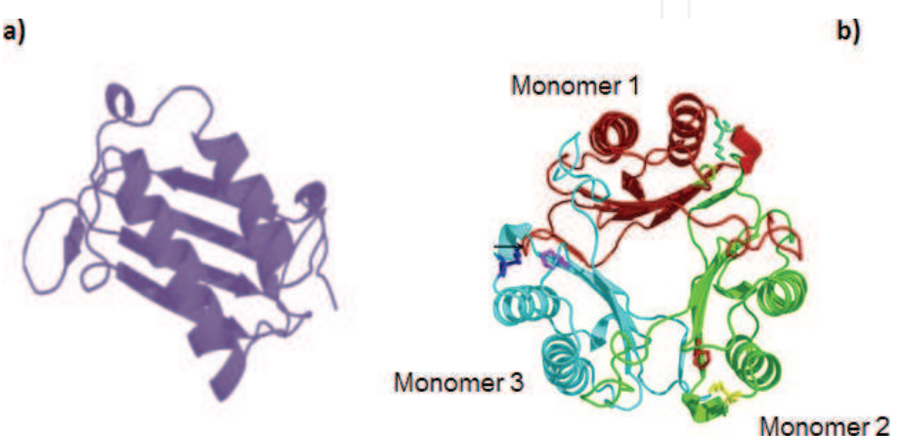

Figure 3.
MIF structure. (a) The folding of the MIF monomer and (b) the folded structure of MIF trimer [18].

stimulates the release of other cytokines, such as TNF-α, IFN-γ, IL-1β, IL-6, IL-8, and IL-12 in inflammation [19].

MIF also participate in the modulation of the expression of other pro-inflammatory molecules, including the same MIF, nitric oxide and cyclooxygenase 2 (COX-2), and prostaglandin 2 (PGE2), perpetuating the inflammatory environment, by positive feedback to the inflammatory response [22, 23].

MIF plays a critical role in the regulation of the innate immune response, through the modulation of TLR4. Activation of TLR4 results in the production of pro-inflammatory mediators, including MIF, which induces the recruitment of inflammatory cells, including neutrophils [19].

3.2 MIF chemotactic activity

Although MIF was identified for the first time as an inhibitor of macrophage migration, subsequent studies revealed that in the presence of inflammatory mediators, it is also capable of leukocyte extravasation [24]. This cytokine can have a similar function to chemokines while it is in interaction with the chemokine receptors CXCR4 and CXCR2 to promote the recruitment of inflammatory cells [19].

In this way, MIF participates in the adhesion of monocytes to the vessel wall and its transendothelial migration [25]. This immobilization of cells to the endothelial surface is mediated by the action of chemokines that prevent these cells from continuing their circulation, promoting the immobilization and transmigration of the cells through the endothelium [26].

3.3 MIF and periodontal disease

The pro-inflammatory, chemoattractant, and osteoclastogenic characteristics of MIF make it a cytokine with an important role both in the initiation and progression of periodontal disease (**Figure 4**).

The studies related to MIF and periodontal disease are few; however, the existing ones have given the guidelines to introduce this cytokine to its pathophysiology.

3.3.1 MIF expression in gingival tissue

As mentioned above, MIF is a cytokine produced by immune and nonimmune cells; therefore the source of MIF in periodontal tissues can be diverse including inflammatory cells as cells resident in tissues [19].

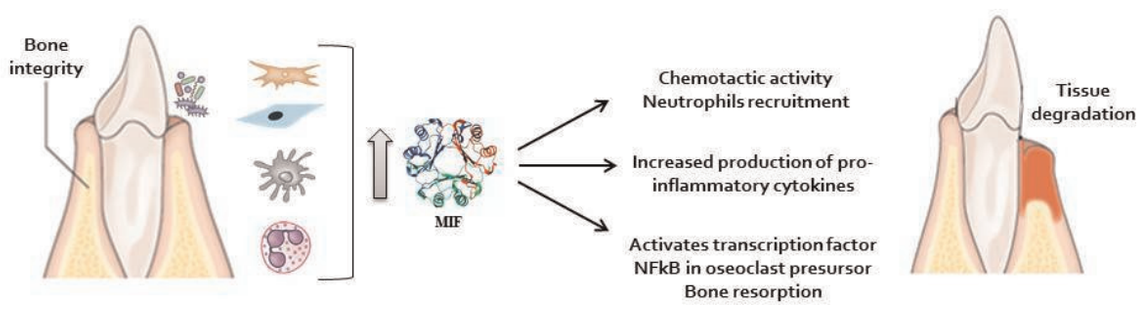

Figure 4.
MIF in periodontal disease.

In 2003, the presence of MIF in epithelial cells, keratinocytes, and fibroblasts of gingival tissue was first described by immunohistochemistry [27], confirming that this cytokine is located preformed in the cytoplasm of the cell [21], therefore MIF could participate in homeostatic, proliferative (necessary for the cell), and inflammatory functions in the tissue [27].

Likewise, Li et al. evaluated the expression of MIF in gum biopsies of subjects with PE where they found the presence of MIF in both epithelial strata and in connective tissue vessels; it was also determined that reconstituted gingival epithelial cells overexpress MIF when performing stimulations with LPS [28]. Therefore, the expression profile of MIF can be regulated by the periodontal conditions and the presence of endotoxins that induce its release [21].

3.3.2 MIF in gingival crevicular fluid

The evaluation of MIF in body fluids as a biological indicator has been carried out in various pathologies. Recently the gingival crevicular fluid (GCF) has received a lot of attention for being an informative fluid of both physiological and pathological events in the oral cavity.

In 2009 the concentrations of MIF in GCF of subjects with induced gingivitis were determined where it is verified that the levels of MIF can be modified in response to bacterial colonization in the gingival sulcus [29], this being the first work in describing the cytokine in this fluid.

Another study evaluated the MIF concentrations in GCF of patients with metabolic syndrome with gingivitis. This study found that the group with both pathologies does not present significant differences with the group that presents only gingivitis; nevertheless, it found differences in comparison with healthy subjects, and therefore the authors related the increase of MIF directly with the gingival inflammation and not with the presence of the metabolic syndrome [30].

3.3.3 MIF in saliva and serum

Research on the quantification of MIF in saliva has been increasing in various pathologies such as oral squamous cell carcinoma [31], in studies evaluating depressive symptoms [32], and in chronic pelvic pain syndrome [33], among others.

The investigations about MIF serum concentrations are extensive because this fluid has been used to evaluate MIF in numerous systemic diseases.

In 2017 MIF was evaluated in saliva and serum in aggressive PE, this study was first to report this cytokine in both fluids in periodontal disease. Their results showed that the cytokine increased significantly due to the presence of the disease in both fluids, likewise MIF correlated with clinical diagnostic parameters [34].

Knowing the concentrations of MIF in different fluids in periodontal disease would provide us the information necessary to know the behavior of the protein at the local and systemic levels in the presence of this type of entity.

3.3.4 MIF experimental studies

An experimental study in a murine model of PE showed that in MIF −/− mice, the absence of MIF decreases the clinical signs of the disease and the recruitment and phagocytic activity of neutrophils. It also points out that MIF is important in the control of infection because the lack of the cytokine increases the bacterial load and decreases the production of inflammatory cytokines in MIF −/− mice compared to wild-type mice [35].

Another study in a murine model of acute apical PE analyzed the coexpression of MIF and RANKL in periapical lesions induced in mice, where the author associates that the presence of MIF increases the pro-inflammatory environment that promotes the overexpression of RANKL, the inducer of the direct activation of the osteoclasts [36].

The osteoclastogenic activity of MIF in PE can also be attributed to the ability of the cytokine to activate signaling pathways such as NF-kB and NFAT in osteoclast precursors that initiate differentiation and survival in the cell [37, 38], as well as the possible chemoattractant faculty of MIF by acting as a ligand for the chemokine receptor CXCR4 in the recruitment of osteoclast precursor cells [39].

4. Conclusion

In periodontal disease MIF regulates the immune response and can promote soft tissue degradation and bone resorption.

Due to the few studies about MIF and periodontal disease it is important to continue doing more research to elucidate the participation of this cytokine in the immunopathology of this disease.

Conflict of interest

The authors declare that they have no conflicts of interest.

Abbreviation

GCF	gingival crevicular fluid
MIF	macrophage migration inhibiting factor
PE	periodontitis
RANK	receptor activator of nuclear factor-kappa B
RANKL	receptor activator of nuclear factor-kappa B ligand

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