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Review Article

B Cells in Periodontitis - A Friend or Foe?

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Abstract

It is evident that B lymphocytes and Plasma cells superior among cells in periodontitis. Despite the fact that T cells work as the principal regulatory group of cells, B cells seem to have several critical roles in periodontitis. The capacity of B cells to demonstrate class II antigens and contribute to antigen presentation has been revealed in periodontal diseases. Different subtypes of B cells, such as B-1a and B-2 cells are present in periodontal lesions. Increased level of B-1a cells has been reported in subjects with severe forms of periodontitis. B-1a cells have been associated with interleukin-10 and this cytokine serves as an autocrine growth factor for this type of B cell. Despite the fact that microbial antigens are associated with the initiation of the inflammatory responses in periodontitis, endogenous antigens also play a part in the chronicity of periodontal disease.

Keywords: Periodontitis; B Cells; T Cells; Bone Loss

Introduction

Periodontitis is characterized by chronic inflammatory lesions linked with tooth-supporting hard and soft tissue destruction resulting from imbalances between the oral microbiome and the host immune response. The dental plaque act as a primary etiological factor for the initiation of the periodontal lesion. The intensity of periodontitis is determined by the balance or imbalance established between the oral biofilm and the inflammatory process [1]. The immune responses in periodontitis emerge as a response to the periodontal pathogen, they might additionally target self-antigens released during the tissue destruction. The prevalence of the periodontal disease correlates with raised antibody responses to pathogenic bacteria indicate that immune response is involved in the initiation of periodontitis and that established immune reaction to periopathogen might play a defensive role. B lymphocytes invade the gingiva in periodontal disease, but it is unclear whether the established immune response to bacteria plays a defensive or a destructive, role in periodontitis. Therefore, this review critically evaluates the various roles of B lymphocytes in periodontal lesions.

Berglundh and Donati., *et al.* described that 70% of cells infiltrating gingiva of periodontal disease includes plasma cells and B lymphocytes (Plasma cells account for 50 % and B cells 20%). Lappin., *et al*. and Thorbert-Mros., *et al*. found that the total percentage of B lymphocytes and plasma cells were elevated during periodontal disease progression. The secretion of inflammatory cytokines and autoantibodies are two possibilities by which B lymphocytes may contribute in pathology of periodontal disease. Han., *et al*. demonstrated that activated B lymphocytes stimulate the secretion of receptor activator of nuclear factor kappa-B ligand (RANKL) which acts as an important mediator for periodontal bone loss.

Antigen-presention by B cells

The antigen presentation by B cells differs to some extent from that of other, antigen-presenting cells, like dendritic cells, macro-

phages, and langerhans cells. The B cells internalize antigens by an immunoglobulin receptor in the cell membrane, while other antigen-presenting cells take up antigens through pinocytosis or internalization of receptors for immune complexes. The antigen is broken down into peptides and thereafter attached to class II molecules of the major histocompatibility complex (Figure 1). Eventually, the prepared antigen is transported to the B-cell membrane for presentation to helper T cells (CD4+). This finding reveals that B cells can induce an immunological response in the absence of either dendritic cells or macrophages and that the CD154 expression on T helper cells is critical for the maturation of B cells into competent antigen-presenting cells [2].

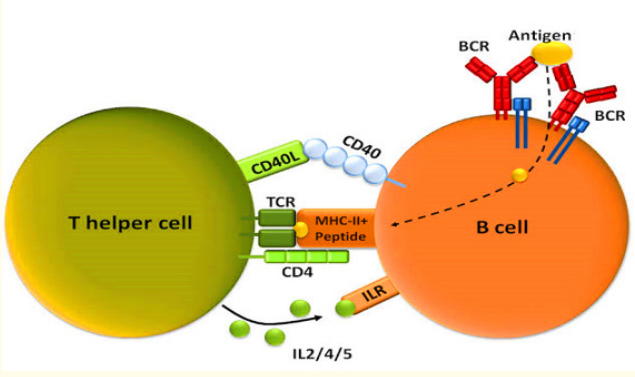

Figure 1: Antigen presentation by B cell.

B Lymphocyte and Plasma cells

Plasma cells and B lymphocytes account for 70 % of total inflammatory infiltrate in the gingival tissue of periodontitis patients and their proportion could be elevated during disease progression. Despite their prevalence in the developed periodontal lesion, the roles of B lymphoctes in periodontitis still unclear. There have been several reports that B lymphocytes in the gingiva of periodontitis patients express the co-stimulatory molecules CD86, CD83, and CD80. There is confirmation that up to twenty two percentages of the plasma cells in the gingiva of periodontitis patients are actively producing antibodies that specially recognize P. gingivalis.

In periodontitis patients, antibody titers against P.gingivalis found to be a consistently higher in disease site than those of clinically healthy site. However, most of the antibody titers against P. gingivalis are incapable of clearance of this bacterium. Additionally, it has been stated that gingipains secreted by P. gingivalis effectively destruct the opsonizing antibodies (IgG1 and IgG3 subclasses). Also, elevated titers of autoantibodies detected in the serum of periodontitis patients, against extracellular matrix component such as collagen type I, fibronectin, and laminin. These anti-collagen antibodies are believed to be involved in the aggressive forms of periodontitis and further leads to progression of periodontal disease. The production of anti-collagen antibodies suggested that B lymphocyte function has become abnormally regulated in periodontitis. Some studies reported that oral bacteria may directly and distinctly regulate B cell function. Experimental studies demonstrated that activated B lymphocyte may exacerbate alveolar bone loss through expression of receptor activator of nuclear factor kappa-B ligand (RANKL) when transferred to the mice infected with A. actinomycetemcomitans. This demonstrates that B lymphocyte function, may be altered after interaction with pathogenic bacteria, and further associated with disease progression. Additionally, different subsets of mature B lymphocyte have been described, which may respond differently to pathogenic stimuli (Table 1).

B Cell subtype	Function
CD138+ plasma cells	Association with the advancing front of the periodontal lesion.
Immunoglobulin-bearing lymphocytes; plasma cells	Clinical progression of the periodontal lesion; Stimulate the expression of RANKL in the gingiva.
Memory	Production of antibodies against periodontal pathogens. To prevent bone loss due to subclinical inflammation in clinically healthy periodontium.
B1	Associated with regulatory functions and the numbers might be decreased in periodontitis patients; produces antibodies against antigens and act as antigen-presenting cells.
Breg/B10	Negatively regulates the inflammatory responses via IL-10.

Table 1: B lymphocyte subtypes.

B cells in Periodontal Homeostasis

Mahanonda., *et al.* reported memory B cells in healthy periodontium and were detected in the extracellular matrix adjacent to the junctional epithelium, which might be due to the local sub-clinical inflammatory reaction to a continuous challenge of the dental plaque. N Dutzan., *et al.* also reported a minimum existence of B

lymphocytes in diseased free gingival sites and such minimal levels may be essential to prevent bone loss in the diseased free periodontium. Another facet of the B lymphocyte biology is the production of antibodies against bacterial antigen, which may lead to host protection. Page., *et al.* stated that immunization by using P. gingivalis as an antigen might reduce the onset and progression of bone loss. Also, Shelburne., *et al*. demonstrated that antibodies against P. gingivalis determine health in patients prone to periodontitis.

B cells in Periodontal Inflammation

Oliver-Bell., *et al.* stated that B lymphocytes create a considerable contribution to periodontal bone loss in PD, most likely due to activation of B cell and expression of receptor activator of nuclear factor-kappa B ligand in the periodontium. Oliver-Bell., *et al*. studied, RANKL expression of activated B cells through P. gingivalis infection, showing that mice infected with P. gingivalis demonstrated a major increase in RANKL expression through B-cell activation within the gingiva. Also, B-cell-deficient mice failed to show P. gingivalis-induced bone loss.

Abe., *et al.* demonstrated that ligature-induced periodontal disease results in to a considerably less periodontal bone loss in B cell-deficient mice, favoring the importance of B lymphocytes in periodontitis. In diseased free periodontium, the memory B cells arrest the bone loss and produce antibodies against bacterial antigens.

Mahanonda., *et al.* in their study, revealed that the consistency of memory B cells in periodontal disease was notably lower than in healthy gingival tissues. On the opposite hand, the proportion of antibody-secreting cells and CD138+ plasma cells were statistically greater than that of memory B cells in periodontitis. The author stated that plasmatocytes were detected at the bottom of the periodontal pocket and scattered toward the advancing front of the lesion. In periodontitis, B cells may contribute to chronic inflammation through the secretion of IL-8 and IL-1β.

Kawai., *et al.* have stated that B lymphocyte is the cellular source of receptor activator of nuclear factor-kappa B ligand in the periodontium which results in bone destruction. Additionally, Malcolm., *et al*. have shown that the proportion of B cells demonstrating RANKL was increased following P. gingivalis infection in periodontal tissues.

Kanzaki., *et al.* demonstrated that tumor necrosis factor-α and soluble receptor activator of nuclear factor-kappa B ligand split from activated TNF-α enzyme-bearing B lymphocytes could be important for bone resorption in periodontitis. Han., *et al*. demonstrated that B cells induce alveolar bone homeostasis in periodontitis through RANKL-dependent and antibody-independent mechanisms.

Demoersman., *et al.* reported that a remarkably higher proportion of CD27+ memory B cells were found in patients with severe periodontitis. Zouali., *et al.* support that B lymphocytes participate in receptor activator of nuclear factor-kappa B ligand mediated bone resorption. On the contrary, blocking receptor activator of nuclear factor-kappa B ligand, and a proliferation-inducing ligand (APRIL) reduce bone loss in animal models of PD.

Coat., *et al.* stated that rituximab acts against protein CD20 of B cells and might be improved periodontal parameters, finalize that anti-B cells treatment might be useful to stop clinical progression of PD. Regulatory B (Breg/B10) cells are one of the subtypes of B cells that negatively regulate the inflammatory responses via IL-10 production thereby exerting a suppressive role in the immune response. B10 cells exist in periodontal tissues of patients with and without periodontitis, but in notably higher levels in periodontal disease sites when compared to healthy sites.

Yu., *et al.* stated that the secretion of IL-10 by B10 cells inhibits the inflammatory alveolar bone loss in ligature-induced experimental periodontitis. Wang., *et al*. conducted experimental periodontitis in mice and concluded that Breg cells significantly inhibit inflammatory bone loss in PD.

Dutzan., *et al.* in their studies, reveal, that a minimum presence of B lymphocytes in diseased free periodontium, leads to less alveolar bone loss

B-cells and tissue destruction

The activation of B lymphocytes that takes place during antigen-specific immune responses results in isotype switching, proliferation, maturation, and differentiation into Ab-secreting plasma cells. Plasma cells also produce cytokines such as tumor necrosis factor-alpha, interlukin-6, interlukin -10, and transforming growth factor-beta. TNF-alpha regulates the turnover of extracellular matrix by inducing the expression of matrix metalloproteinase, while TGF-beta down-regulates the synthesis and secretion of these matrix metalloproteinase (MMPs) and promotes the production of their inhibitors (tissue inhibitors of matrix metalloproteinase/TIMPs).

Plasma cells detected adjacent to blood vessels express the VEGF, which in turn stimulates matrix metalloproteinase activa-

tion and angiogenesis. The activity of matrix metalloproteinase in diseased free tissues is low but increases considerably in diseased conditions results in tissue destruction. Abundant lymphocytes of the B-cell series, including plasma cells, are present in the dense mononuclear inflammatory infiltrate in the diseased gingival tissue which makes periodontal disease different from both gingivitis and other infection-related inflammatory lesions. It was found that B-cells along with T-cells were the major cellular sources of RANKL, producing evidence that B-cells not only produce bacteria-reactive immunoglobulin-G (IgG) but also contribute to pathogenic processes of periodontal bone destruction.

In periodontitis, the stimulation of particular B-cell subtypes and their cytokine production are key element in determining whether the inflammation will subside or advance to destructive periodontitis.

Immunoglobulin-dependent pathogenic pathways in periodontitis (Figure 2)

Autoimmune responses are involved in periodontal disease and several autoimmune components, such as autoreactive B cells and autoantibodies, were observed in periodontitis. Collagen type I act as one of the main evaluated autoantigens. Higher levels of antibodies to type I collagen was found in the peripheral blood of patients with periodontal disease than in healthy controls. Increased reactions of immunoglobulin G to desmosomal proteins were detected in patients with periodontitis in comparison to controls. Anti-phospholipids antibodies, which are normally found in SLE patients, have also been detected in subjects with different forms of periodontitis. Autoantibodies might act on T lymphocytes and other cells and facilitate inflammatory cytokine secretion. This process might be involved in the periodontal disease initiation and progression.

Immunoglobulin-independent pathogenic roles in chronic inflammatory periodontal disease (Figure 3)

B lymphocytes provide with innate-like functions, such as B-1a and MZ (marginal zone) B lymphocytes, possess autoreactive and host-damaging potentials as opposed to the conventional "B2" cell subset [3-6]. In patients with periodontal disease, the assignment and proliferation of B-1a cells in the gingiva might be observed. Some studies reported that the prevalence of CD5+ B cells, i.e., B-1a cells, in inflamed gingival tissues were increased in periodontitis patients compared to healthy subjects [7]. The CD5+ B cells were found in the connective tissues from the middle part to the apical

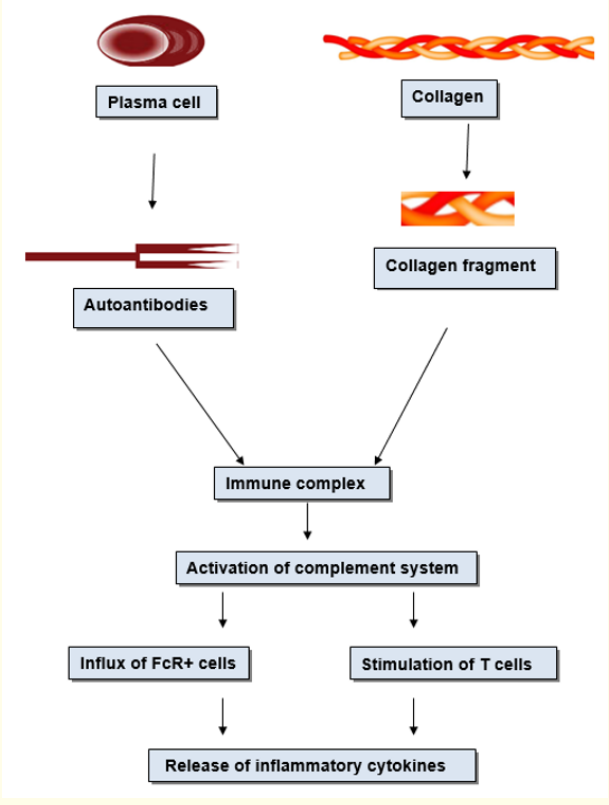

Figure 2: Immunoglobulin-dependent pathogenic pathways in periodontitis.

IgG autoantibodies could contribute to formation of immune complexes with fragments of collagen, and, subsequently, activate the complement system and promote influx of polymorphonuclear cells that express Fc receptors.

portion of the periodontal pocket and this area reveals the destruction of extracellular matrix along with dense cell infiltrations. Also, flow cytometry analysis revealed that B-1a cells found in significantly higher proportion in PD than diseased free subjects [8].

In periodontitis patients, the percentage of B-1a cells were found to be a 5 to 6 times greater compared to healthy subjects, and up to 40–50% of CD19+ B cells were positive for the B-1a cell CD5 marker [9-11]. Since higher percentage of B-1a cells and interleukin-10 were seen in the gingival tissue than in peripheral blood, it was concluded that B-1a cells are activated in PD [12]. The interlukin-10, activates B lymphocytes and act as an autocrine growth factor for B-1a cells [13]. Also, bacterial antigen initiate an interlukin -10 response that results to the differentiation of B-1a cells

and autoantibody secretion. It has been reported that elevated level of B-1a cells may represent a marker of PD susceptibility rather than an indicator of the presence of the disease [14,15].

The experimental studies suggest that B-1a cells participate in the immune reaction seen in patients with periodontal disease. They are the principal source of self-reactive antibodies seen in PD. Further, exaggerated and atypical activation of B lymphocytes may take part in disease progression by presenting antigens by producing inflammatory cytokines. B cells may possess roles in bone metabolism through secretion of osteoclastogenic factors and expression of RANK [16-18].

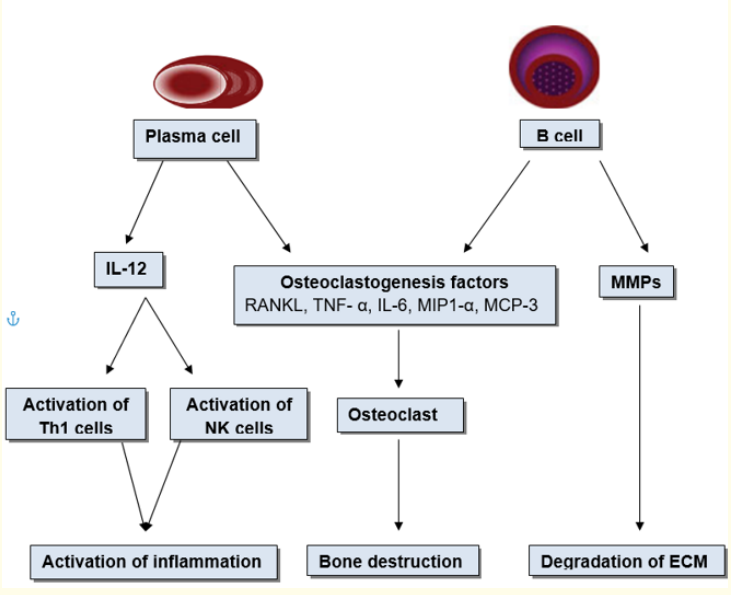

Figure 2: Immunoglobulin-independent pathogenic roles of B cells in periodontitis.

Conclusion

As discussed above, experimental studies investigate that B lymphocytes take part in biofilm-induced alveolar bone destruction. Studies demonstrated that B lymphocytes, plasma cells, and bone resorption factors (receptor activator of nuclear factor-kappa B ligand, OPG) and particular cytokines such as B cell-activating factor/a proliferation-inducing ligand takes part in the initiation of bone loss in PD. It is essential to know about the secretion and function of B lymphocytes, altered concentration of osteoprogerin, receptor activator of nuclear factor-kappa B ligand, and B cell-activating factor/a proliferation-inducing ligand during disease progression which will further allow to understand the exact mechanisms of B lymphocytes in periodontal health and disease. Experimental studies reported that activated- receptor activator of nuclear factor-kappa B ligand -positive B lymphocytes results in exaggerated periodontal bone destruction. Therefore, blocking of this osteoclastogenic factors will help to decrease bone loss in PD. Further studies need to be conducted to build-up inventive treatment modalities for PD associated with atypical B lymphocytes function. The various roles of B cells in periodontal disease require further elucidation for the understanding of the tissue mechanisms involved in the initiation and progression of the disease.

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