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The Role of Innate and Adaptive Immune Responses in The Pathogenesis of Periodontitis: A Narrative Review

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Abstract

Periodontitis is a complex disease that attacks periodontal tissue by progressive damage caused by various factors lead to inflammatory process. The progression of periodontitis is associated with bacterial activity that induces an inflammatory response in the host. Changes in the composition of bacteria within dental plaque leading to increased inflammation of the periodontal tissue which triggers the activation of inflammatory mediators from the host. Relative studies were identified and collected through case report and review article in Medline/Pubmed, Sciencedirect, Wiley Online Library and Google Scholar websites from 2011 until 2024. In addition to producing a chronic inflammatory process, periodontitis induces immune system dysregulation, which leads to microbial dysbiosis in the subgingival and submarginal locations. Both the humoral and cellular components of the innate and adaptive immune systems are plays crucial role for periodontitis. Periodontitis is a chronic disease and an advanced stage of gingivitis, when the immune system fails to counter bacterial invasion, the inflammatory process persists, and leading to extensive damage to periodontal tissues.

Key words: Adaptive Immunity, Innate Immunity, Immune Response, Periodontitis

1. Introduction

A disease of the tooth-supporting tissues or periodontal tissue, periodontitis is characterized by gradual deterioration brought on by various factors that trigger an inflammatory response.[1] Loss of periodontal ligament attachment and alveolar bone resorption, which exposes tooth roots, are signs of damage to the supporting tissues.[2] Severe periodontitis ranks as the eleventh most common disease globally, according to statistics from the Global Burden of Disease Study.[3] Furthermore, the most frequent cause of adult tooth loss, according to the World Health Organization, is periodontitis.[4]

Bacterial activity is linked to the development of periodontitis, which causes the host to become inflamed. Alterations in the bacterial composition of dental plaque cause the periodontal tissue to become more inflamed, which triggers the host's inflammatory mediators.[5] Tissue injury, junctional epithelium movement, and the formation of bacterial biofilms in an apical orientation are all influenced by elevated host-derived proteinases.[6] Despite various studies on periodontitis pathogenesis, the integrated role of both innate and adaptive immunity in progressive stages of disease remains to be clearly synthesized. This review aims to explain and understand the immune response that contributes to the inflammatory stages of periodontitis.

2. Method

Data were identified and collected through case report and review article in Medline/Pubmed, Sciencedirect, Wiley Online Library and Google Scholar websites until 2024, the selected articles used have been published in accredited scientific journals and have gone through a peer-reviewed process. Free text words were used for searches with the words used "adaptive', 'innate' 'immunity', 'periodontitis'. Reference lists of all articles obtained from data sources were selected for further follow-up. To confirm the quality and relevance of the articles obtained, limited use according to the criteria was used. Articles that met the inclusion criteria were included. Articles published before the year 2011 or no relevant to issue will be excluded from the review. The use of this search source provides a wider source to be used as research data and can provide an in dept and up to date analysis immune response on periodontitis.

3. Result and Discussion

Periodontitis

Periodontitis is a complex disease that attacks periodontal tissue caused by various factors, including genetic predispositions, and others are modified from patient behavior, medical treatment, or environmental factors. In addition, periodontitis can also be exacerbated by individual risk factors.[7]

According to population epidemiological surveys, the prevalence of severe periodontitis can range from 10% to 15% in nations with inadequate dental care, while it can reach 20% among racial or ethnic groupings, such as the African population.[8]

Inflammation causes tissue damage to the periodontal tissue, which includes the gingiva, periodontal ligament, cementum, and alveolar bone. This is followed by a phase of cell proliferation in soft tissue and remodeling in hard tissue.[9] Age, genetics, and comorbidities that affect immune system function all affect the stages of periodontitis and hemostasis damage in periodontal tissues during the course of a lifetime.[10]

Periodontitis attacks periodontal tissues, generally initiated by specific bacteria found in dental biofilm, but the signs and symptoms experienced by patients depend on the individual's immune response to bacteria and their product.[11] The characteristics features of periodontitis can be assessed from the excessive, non-specific and ongoing inflammatory process in periodontal tissues.[7] If left untreated prolonged inflammation leads to host-mediated damage in soft tissues, hard tissues and alveolar bone.[12]

Mediator and Cell Inflammation

Based on previous studies, excessive immune response to bacteria in periodontal tissue is the primary cause of the pathogenesis of periodontitis.[13] The elements contributing to the development of periodontitis are categorized into two groups, those from subgingival bacteria known as microbial virulence factors and that arise from the host's inflammatory response. [11,14]

The elimination of invading pathogens relies on the synchronized efforts of the innate and adaptive immune systems. The adaptive immune system specifically focuses on pathogens and requires days to weeks, whereas the innate immune system offers immediate defense against pathogens.[15,16] Alongside the humoral elements of the innate and adaptive immune systems in periodontitis, cellular components also significantly contribute to its progression. [11,14,17,18]

Table 1. Mediator of Inflammatory In Periodontitis

Source	Mediator Inflammation	Roles
Microbial virulence factor	Lipopolysaccharides	Increased production of inflammatory mediators mostly cytokines
	Microbial invasion (*Porphyromonas gingivalis, Aggregatibacter actinomyceremcomitans, Fusobacterium nucleatum).*	Invade host cell (epithelial cell), inhibition of Interleukin-8 secretion
	Fimbriae	Toll-Like Receptor-2 triggers immunological responses, including the release and suppression of interleukin-6 and interleukin-8. Macrophages' release of interleukin-12
	Bacterial Deoxyribonucleic Acid (DNA) and Extracellular Deoxyribonucleic Acid	Through Toll-Like Receptor-9 stimulates immune responses
Host-derived inflammatory mediators	Cytokines	Proteins that are soluble and serve as messengers to move signals between cells. Cytokines start intracellular signaling by attaching to particular receptors on target cells.
	Prostaglandins	Group of lipid compounds from arachidonic acid, PGE_2 induces vasodilation, cytokine production and bone resorption
	Matrix metalloproteinases (MMPs)	Group of enzymes that degrade the body's structural protein

Table 2. Role of Inflammatory Mediators In Periodontitis

Types	Nomenclature	Roles
Pro-inflammatory Cytokines	Interleukin-1α	Intracellular protein, proinflammatory, aids in bone resorption, and acts as an intracellular transcriptional regulator
	Interleukin 1β	Important role in inflammation and innate immunity collaborates with additional proinflammatory mediators that play a significant role in adaptive immunity, promoting the degradation of connective tissue and the resorption of bone
	Interleukin-1Ra	Blocks the activity of Interleukin-1α and Interleukin-1β
	Interleukin-18	Similar proinflammatory characteristics to IL-1β, stimulates neutrophils, collaborate with Interleukin-12 to stimulate T-h1 cells
	Interleukin-33	Stimulates of T-h 2 cells and mast cells, serve as an intracellular transcriptional regulator but with limited expression
	Interleukin-6	Crucial function in managing the development and maturation of B cells and T cells
	Interleukin-17	Initiate inflammatory reactions

	Tumor Necrosis Factor-α	Enhances neutrophil activity and facilitates cell and tissue renewal by promoting MMP
	Interferon-ɣ	Stimulates NK cells, macrophages, and cytotoxic T cell
Anti-inflammatory cytokines	Interleukin-10	Inhibit T h-1 and T h-2 cytokine production
	Tumor Growth Factor-β	Regulation of T-cell subtype and the function of Treg cell, and contributing to repair and regeneration
Matrix Metalloproteinases	Collagenases MMP-1	Keratinocyte migration and re-epithelialization, platelet aggregation
	Gelatinases MMP-2	Migration of epithelial cells and differentiation of mesenchymal cells with an inflammatory phenotype
	Stromelysins MMP-3	Impaired cell aggregation, enhanced cell penetration
	Matrilysins MMP-7	Impaired cell aggregation, enhanced cell penetration
	Membrane-type MT1-MMP	Migration of epithelial cells, breaks down collagen types I, II, and III
Complement	C1-C9	inflammatory cells' recruitment and activation (via the anaphylatoxins C3a and C5a, which engage with certain G-protein-coupled receptors on leukocytes)
		Microorganisms opsonize (using opsonins like C3b) to aid in phagocytosis
		Direct destruction of specific bacteria (through the C5b-9 membrane attack complex)
Antibody	IgG	Antigen neutralization
	IgM	Antigen neutralization
	IgA	Antigen neutralization

Pathogenesis Periodontitis

Periodontitis is a complex chronic disease that leads to immune system dysregulation, in addition to causing a continuous inflammatory process, an excessive immune response triggers microbial dysbiosis in submarginal and subgingival sites.[7] Healthy periodontal tissue is dominated by gram-positive commensal bacteria; however, the accumulation of bacteria induces an inflammatory response from the host. Persistent inflammation causes tissue damage and bleeding which provides proteins such as hemin (an iron source) that favor gram-negative bacteria, exacerbating inflammation.[10]

Gingivitis, or inflammation of the gingiva, is the first stage of periodontitis. As a source of energy, saccharolytic gingival bacteria break down the proteins in gingival crevicular fluid, releasing ammonium as a byproduct in the process. *Porphyromonas gingivalis* and *Prevotella intermedia* are the two bacteria most frequently linked to periodontitis.[19] Increased gingival crevicular fluid comprising collagen breakdown products and immune response products such complement, immunoglobulins, serum proteins, cytokines, and chemokines are the outcomes of the gingiva's inflammatory reaction.[20]

Table 3. Role of component cellular in periodontitis

Component	Cell	Roles
Innate Immunity	Polymorphonuclear neutrophils	Primarily involved in phagocytosing/microbial killing
	Macrophages/monocytes	Extremely sensitive to outside stimuli and involved in the host's defense against microbes by phagocytosis, microbial destruction, and MHC-II antigen presentation
	Natural Killer	In addition to direct cytotoxicity in infected cells with low MHC-I, it can mediate antibody-dependent cell-mediated cytotoxicity. possess the ability to modulate B cell function, stimulate IgG, and activate other immune cells through the release of cytokines
	Dendritic cell	Antigen-presentation (via MHC-II and cross-presentation via MHC-I) and activation of adaptive immunity in periodontal tissues
Adaptive Immunity	T-helper lymphocytes	By affecting the chemotaxis and activity/phenotype of other immune cells, T helper lymphocytes can contribute to host defense against pathogens and inflammatory healing processes because of their phenotypic responsiveness to stimuli from the microenvironment
	Cytotoxic T cells	MHC-I-mediated cytotoxicity, immunoregulatory activities linked to inflammatory mediators, and a response to various phenotypes based on environmental stimuli are characteristics of cytotoxic T cells that impact their activity and the profile of inflammatory mediators they emit
	B lymphocytes	Primary role in humoral immunity by producing antibodies, but also can phagocytose, present antigens to T cells and differentiate into osteoclasts

According to Page and Schroeder, the histological changes occurring in gingival tissue due to inflammation are divided into four stages: initial, early, established, and advanced lesions.[11] Early inflammation in periodontal tissue shows signs of physiological defense against bacteria rather than pathological activity. The clinical features at the initial stages comprise supragingival and subgingival plaque, typically succeeded by calculus development and inflammation of the gingival.[14]

The initial lesions are caused by the response of resident leukocytes and endothelial cells to bacterial biofilms. Histologically visible tissue is present at this stage, but there are no clinical indications of inflammation. Bacterial metabolic products cause local blood vessels to dilate by stimulating the production of cytokines by junctional epithelial cells and neuropeptides by neurons. In reaction to chemokines, neutrophils leave the blood vessels and go to the site of inflammation. [14]

Increased vascular permeability, vasodilation, gingival crevicular fluid flow, neutrophil counts in the connective tissue, and the presence of complement, macrophages, lymphocytes, and plasma cells are all indicators of an early lesion. As the epithelium grows, histologically visible rete pegs are formed, and bleeding and other clinical indicators of inflammation start to show up. [21]

The established lesion stage, which follows, marks the change from an innate to an adaptive immune response. IgG from B

lymphocytes is also present in the tissue, and macrophages, plasma cells, and T and B lymphocytes take over.[22] Collagenolytic activity rises and blood flow is disrupted. Moreover, fibroblasts produce more collagen as well. Gingival bleeding, changes in gingival color and contour, and moderate to severe gingivitis are clinical characteristics of this stage. The last stage, referred to as advanced lesion, it is when gingivitis turns into periodontitis. It is evident from both histology and clinical observations that bone loss and attachment loss are permanent. Alveolar bone resorption results from the deeper inflammatory lesions. [14,20,21]

Diagnosis and Therapy of Periodontitis

Based on inflammation, periodontitis can be assigned by gingival index. The gingival index, which measures the extent of soft tissue inflammation and bleeding by employing gentle pressure during periodontal probing, is the most commonly used validated index in clinical periodontal care.[14]

Score 0 : There are no visible signs of inflammation.

Score 1 : A slight variation in texture and color.

Score 2 : When the probe is run along the gingival margin, there is a visible inflammatory and bleeding tendency from the gingival margin.

Score 3 : Severe inflammation with a propensity for bleeding on its own.

The score is given to the buccal, oral, mesial, and distal regions of each of the six index teeth (maxillary left first premolar and maxillary right first molar, lateral incisor; mandibular right first molar; mandibular left first molar and lateral incisor) in order to assess the gingival index at the patient level. The patient's Gingival Index score is calculated by averaging the scores of the various locations.[14,23]

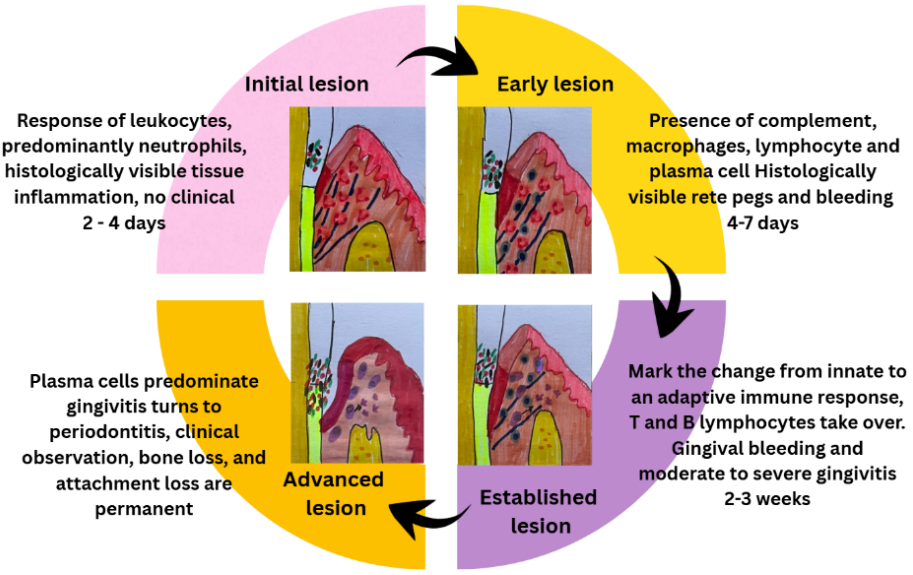

Figure 1. Histological changes in periodontitis according to page and schroeder [14]

Diagnosis and therapy can also be guided by the stage of periodontitis. The changes in immune response during the established lesion of periodontitis represent a critical shift influencing the prognosis, indicating whether the lesion will become progressive or not. The established lesion stage signifies that the patient's inflammation has reached a chronic phase. Chronic inflammation in periodontitis is characterized by a dominance of B lymphocytes, which contribute to alveolar bone destruction.[14] Non-specific treatments, such as scaling and root planning, are no longer sufficient. The addition of host modulation therapy (HMT) can be considered, aiming to reduce tissue destruction and promote regeneration of periodontal tissues by modifying the host immune response and regulating tissue repair mechanisms. Pharmacological treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) can be used to inhibit pro-inflammatory cytokines, also tetracyclines, that can be used as antibiotics and inhibit matrix metalloproteinases (MMPs) which degrade collagen in periodontal tissue.[14,24]

4. Conclusion

Periodontitis is a chronic disease and an advanced stage of gingivitis. When the immune system fails to combat bacterial invasion, the inflammatory process continues leading to more extensive damage to the periodontal tissue. The progression of periodontitis can be observed not only clinically but also histologically, marked by changes in immune components. Initially, periodontitis is dominated by innate immune response, such as neutrophils, macrophages, and pro-inflammatory cytokines to adaptive components, including an increased number of T lymphocytes, B lymphocytes, and antibodies. These changes in immune markers of periodontitis can serve as a reference to diagnose the stages of periodontitis progression and therefore the therapy.

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