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IMMUNOLOGICAL ASPECTS OF PERIODONTAL DISEASES: A REVIEW

Dentistry

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ABSTRACT

Periodontal disease is recognized as a major public health problem throughout the world and is the most common cause of tooth loss in adults. Although periodontal disease is of microbial etiology, the determination that periodontal tissue destruction is primarily due to the host response, has created areas of research directed at altering an individual's reaction to the bacterial challenge. This article will be focusing on various aspects of immunology in periodontal diseases such as immunity itself, cells of the immune system, leukocyte functions, molecular biology, inflammatory mediators of the immune system, osteoimmunology and immunology in various periodontal diseases.

KEYWORDS

Immunity, Periodontal diseases, Hostmicrobial, Osteoimmunology, Leukocyte.

INTRODUCTION

Periodontal disease is a chronic bacterial infection that affects the gingiva and bone that supports the teeth. There are some immunological factors involved in the development and control of this oral disease, such as: the participation of inflammatory cells in local inflammation, the synthesis of chemotaxis proteins with activation of the complement system and a range of antimicrobial peptides, such as defensins, cathelicidin and saposins. An individual's susceptibility to periodontitis may be related to whether plasma cells predominate in the tissues of an individual, or a site, in response to the microbial insult from dental plaque. Various features that play role in immunological responses may include homing of immune and inflammatory cells to target tissues, their local proliferation and synthetic activity, the cytokine profile; and the immunoglobulin subclasses of locally produced antibodies.

Role of innate immunity in periodontal diseases

Defenses against infection include a wide range of mechanical, chemical and microbiologic barriers that prevent pathogens from invading the cells and tissues of the body. Saliva, Gingival Crevicular Fluid and the epithelial keratinocytes of the oral mucosa all protect the underlying tissues of the oral cavity and the peridontium. The commensal microbiota (e.g., in dental biofilm) may also be important for providing protection against infection by pathogenic microorganisms through effective competition for resources and ecologic niches and also by stimulating protective immune responses.

Aspects of innate immunity that are relevant to periodontal disease are now considered.

Epithelial Tissues

The epithelial tissues play a key role in host defense because they are the main site of the initial interactions between plaque bacteria. The keratinized epithelium of the Sulcular and gingival epithelial tissues provides protection for the underlying periodontal tissue in addition to acting as a barrier against bacteria and their products.[2,3]

Saliva

The action of shear forces associated with saliva flow is important for preventing the attachment of bacteria to the dentition and oral mucosal surfaces. Human saliva also contains numerous molecular components that contribute to host defenses against bacterial colonization and periodontal disease such as Antibodies (e.g., immunoglobulin A), Histatins, Cystatins, Lactoferrin, Lysozyme, Mucins and Peroxidase. Gingival Crevicular Fluid GCF originates from the post-capillary venules of the gingival plexus. It has a flushing action in the gingival crevice, but it also likely functions to bring the blood components (e.g., neutrophils, antibodies, complement components) of the host defenses into the sulcus.[2] The flow of GCF increases in inflammation.[4] One of the primary challenges of the innate system is the discrimination of pathogens from host. This challenge is met by recognition of the evolutionary structures: The PRRs (Pattern Recognition Receptors) that bind Pathogen Associated Molecular Patterns (PAMPs), found in a broad type of organisms.

On the basis of function PRRs are classified as:

Signaling PRRs

1. Toll-like receptors
2. NOD receptors (Nucleotide-Oligomerization domain)

Endocytic PRRs

1. CLRs (C-type lectin receptors)
2. RLRs (RIG-1 like receptors)

On the basis of location PRRs are classified as:

1. Membrane bound PRRs
2. Cytoplasmic PRRs
3. Secreted PRRs

Toll-Like Receptors

Toll-like receptors are the gate keepers of innate immunity. TLRs can be divided into five subfamilies : TLR2, TLR3, TLR4, TLR5 and TLR9. TLRs are expressed in the peridontium in health and disease. Both commensal and pathogenic periodontal bacteria stimulate TLR-2 signaling.[5] Over-production of proinflammatory cytokines due to chronic stimulation of tolllike receptors may lead to tissue destruction.[6]

Lipopolysaccharide Binding Protein/ CD14

The concentration of soluble CD14 receptor in saliva and the systemic level of the soluble form of CD14 is significantly increased in patients with periodontal disease and showed severity dependence with increasing levels of periodontal breakdown. Significantly lower levels of the soluble CD14 protein were observed at sites with advanced attachment loss, indicating a protective effect for Cd14.

Nucleotide-binding oligomerization domain –like receptors

Clinical investigations have demonstrated that both NOD1 and NOD2 are expressed in human oral epithelium, gingival fibroblast cells and periodontal ligament. In an investigation it was found that mice deficient in NOD2 showed comparable levels of alveolar bone resorption, whereas mice deficient in NOD1 demonstrated reduced levels of alveolar bone loss when compared with wildtype control mice.

Role of Complement System in Periodontitis

In the context of periodontal inflammation, complement subversion appears to play a major role in periodontal pathogenesis. The

dysregulation of complement activities may lead to a failure to protect the host against pathogens and amplify inflammatory tissue damage. Activated complement components are found at higher levels in the gingival crevicular fluid of periodontitis patients as compared with healthy subjects. Local complement activation may promote periodontal inflammation predominantly via C5a-induced vasodilation, increased vascular permeability and flow of inflammatory exudate, and chemotactic recruitment of inflammatory cells, especially neutrophils.

Role of neutrophils in periodontal diseases

Neutrophils are thought to be key players in host-mediated inflammatory tissue injury in periodontitis and can be found in great numbers in the gingival crevice (≥ 95% of total leukocytes). Extravasating neutrophils enter the gingival crevice through the junctional epithelium which, under inflamed conditions, is largely occupied (by about 60%) by trafficking neutrophils. Neutrophils are attracted to infected periodontal tissues by chemoattractants released from bacteria, host cells or degraded tissue. The number of neutrophils increases from -7 x 104 to -20 x104/ml during the conversion of a healthy sulcus into a diseased gingival pocket.

Role of mast cells in periodontal diseases

Mast cells are key elements in the innate immune system and are located throughout the body in close proximity to epithelial surfaces, near blood vessels, nerves and glands, placing them at strategic location for detecting invading pathogens. Mast cells express a number of receptors that allow them to recognize diverse stimuli. In sensitized individuals, IgE is bound to Fcε receptors (fragments crystallizable epsilon receptor) expressed on the mast cell surface and binding of antigen to surface bound IgE induces mast cell activation.

Role of dendritic cells in periodontal diseases

Dendritic cells, including Langerhans cells and dermal dendritic cells are found in gingival tissue and mature CD83+ dendritic cells are present in tissues from patients with periodontitis. It was also reported that P. gingivalis and A. actinomycetemcomitans stimulated dendritic cells promote a rapid IFN- γ (Interferon gamma) response by stimulating NK cells.

Microbial Virulence Factors

The sub-gingival biofilm initiates and perpetuates inflammatory responses in the gingival and periodontal tissues and their primary importance in periodontal pathogenesis is that of activating immune–inflammatory responses that, in turn, result in tissue damage.

1. Bacterial Enzymes and Noxious Products: These include noxious agents such as ammonia (NH3) and hydrogen sulfide (H2S), as well as short-chain carboxylic acids such as butyric acid and propionic acid.
2. Microbial Invasion Periodontal pathogens such as P.gingivalis and Aggregatibacter actinomycetemcomitans have been reported to invade the gingival tissues, including the connective tissues.
3. Fimbriae The fimbriae of certain bacterial species, particularly P. gingivalis stimulate immune responses, such as IL-6 secretion and the major fimbrial structural component of P. gingivalis, FimA, has been shown to stimulate nuclear factor (NF)-κB and IL-8 in a gingival epithelial cell line through TLR-2.
4. Bacterial Deoxyribonucleic Acid and Extracellular

Deoxyribonucleic Acid

Bacterial deoxyribonucleic acid (DNA) stimulates immune cells through TLR-9. Extracellular DNA (eDNA) is a ubiquitous constituent of all biofilms and of particular interest in biofilms associated with chronic diseases such as periodontitis.

Host-Derived Inflammatory Mediators

Cytokines
Prostaglandins
Matrix Metalloproteinases

Role of adaptive immunity in periodontal diseases

In addition to the innate immunity, adaptive immunity cells and characteristic cytokines have been described as important players in the periodontal disease pathogenesis scenario.

Parts of the adaptive host response in periodontitis as outlined are:

(1) The nature of the lymphocyte type (T and B cells)
(2) Antigen recognition by TCRs
(3) Cytokine profiles of T helper (Th) cells
(4) Autoimmune reactions that may influence the adaptive host response in periodontitis.

T-Cells in Periodontitis

It's evident that both T cells and B cells are present in periodontal disease. It has been hypothesized that T cells are present in more stable lesion of periodontitis while B cells and plasma cells are present in more progressive lesion.

CD4+ T-cells were subdivided initially into two subsets, designated T-helper 1 and T-helper 2, on the basis of their pattern of cytokine production. T-helper 1 cytokines have been associated with infectious inflammatory bone destruction. T-helper 2 cytokines are described to minimize bone loss. The discovery of new T-helper subsets with prominent roles in the modulation of host responses determined the re-examination of T-helper 1/Thelper 2 dichotomy paradigm in chronic inflammatory diseases, including periodontal diseases.

B-Cells in Periodontitis

B cells serve as a well-controlled part of the adaptive host response and act on systems regulated by T cells. Different subsets of B cells, such as B-1a and B-2 cells are present in periodontitis lesions. Elevated levels of B-1a cells have been demonstrated in both periodontitis lesions and peripheral blood of subjects with severe forms of periodontitis. Different pathologic functions of B-1a cells have been associated with IL-10 and this cytokine serves as an autocrine growth factor for this type of B cells.

Osteo-immunology in periodontal diseases

When the response becomes chronic, adaptive immune cells invade the tissue and the inflammatory reaction becomes firmly established, flooding the periodontium with additional bioactive proinflammatory molecular signals (cytokines, chemokines, enzymes, ROS (reactive oxygen species), bacterial products and metabolites, etc.). The accumulation of these molecular signals in the tissue facilitates the spreading of the inflammation to the underlying bone and tamper with the bone homeostasis signaling system, tilting the balance of bone metabolism favoring resorption over formation.

Immunology in Periodontal Diseases

Gingivitis

It is a primary response to the bacteria in plaque. It includes a vascular response with increased fluid accumulation and inflammatory cell infiltration. The early response is mostly lymphocytic, represented by T cells, which is slightly higher. Acute phase protein including α2 macroglobulin, α1 anti trypsin and transferrin are increased with gingival inflammation reflecting the locally stressed environment. Result of a study by Kinane et al indicate that IL-1 levels in GCF increase with plaque and peak levels of this mediator precede clinical sings of inflammation in experimental gingivitis.

Chronic Periodontitis

Extensive studies have been performed examining the characteristics of the inflammatory infiltrate in chronic periodontitis. The distribution of gingival mononuclear cells has shown plasma cells (5% to 15%) in chronic periodontitis. The plasma cells are predominated by IgG followed by IgA in tissues from chronic periodontitis. Moreover, IgG cells in the gingival tissues were identified as IgG1 > IgG2 > IgG3 > IgG4 and IgA1, with high level IgA2 cell levels in advanced lesions. A large number of B cell lineage cells in gingival tissues present a phenotype that can strongly stimulate auto reactive T cells. The TH/TS (T helper and T suppressor) ratios are reduced in chronic periodontitis periodontal lesions. The lower CD4/CD8 ratios, low responses to mitogens and higher expression of HLA-DR (human leukocyte antigen DR isotype) on CD8+ T cells have been suggested to be regulators of periodontal progression. Recently, NK cells have been identified in the gingiva of periodontitis (3% to 7%) in association with damaged fibroblasts. Finally, evidence has suggested a depressed functional activity of cells from gingiva in periodontitis in response to mitogenic stimulation. These findings are consistent with an altered immune cell distribution, immunoregulation and/or function that may contribute to the progression of periodontitis.

Extensive studies have been reported that PgE2 levels are increased in periodontitis when compared to healthy sites with respect to IL-1, investigations have shown:

1) IL-1α and IL-1β activity in > 70% of GCF.

2) IL-1β levels appear higher in GCF from chronic periodontitis when compared to healthy sites and active sites verses inactive sites, which decrease after treatment.
3) IL-1β and cells producing this cytokine are elevated in tissues of chronic periodontitis and are detected in the lamina propria of these tissues.
4) Most studies were unable to document a relationship between IL-1β and the clinical parameters (ie, probing depth, gingival index, bone resorption) of the site.

Aggressive Periodontist

The prevalence of a humoral immune response to A.actinomyc etemcomitans is elevated in patients with localized aggressive periodontitis. Numerous mechanisms of serum mediated bacterial killing are proposed, including lysis by the membrane attack complex of complement and antibacterial substances such as lysozymes. Generalized aggressive periodontitis is often characterized by defects in either neutrophils or monocytes.

There are two neutrophilic function defects i.e. impaired neutrophil function and hyperactive neutrophil function. Selectins and Integrins play a key role in the initial adhesion of neutrophils, thus facilitating transendothelial migration. Peripheral and GCF neutrophil CD18/CD11a and CD18/CD11b expressions have been compared in aggressive periodontitis patients and healthy patients in various studies. It has been demonstrated that neutrophils from patients with aggressive periodontitis have increased intracellular levels of β-glucoronidase, which is present in azurophilic granules of the neutrophils.

Severe periodontal manifestations are also associated with congenital neutropenia, cyclic neutropenia, leukocyte adhesion deficiency type I and type II, glycogen storage disease, Ehlers–Danlos syndrome and Cohen syndrome. There is also a report of aggressive periodontitis associated with Fanconi anemia. Fanconi anemia is an autosomal recessive disorder affecting all bone marrow elements and is associated with cardiac, renal and limb malformations as well as with dermal pigmentary changes. [11]

CONCLUSION

Present knowledge favors the concept that oral bacteria and their metabolic products are the major etiologic factors in the pathogenesis of periodontal disease, although the exact nature of this host-parasite interaction is still incompletely understood. However, a great deal of evidence now suggests that the host's immunologic responses to microbial products are primarily responsible for the development of this disease. In periodontal disease, the inflammatory response causes tissue resistance to bacterial invasion but also provides mechanisms that contribute to tissue damage.

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