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Review Article

Immunity and its Role in Health and Disease: A Literature

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Abstract

The term periodontal diseases describes inflammation of the tissues that offer support to the teeth. It has been recognized that though the bacteria present in plaque initiates the periodontal inflammation, the host response to these pathogens equally matters in the progression of the disease. The immune cells participate jointly through the release of their molecules and mechanisms of action in order to maintain homeostasis in periodontal tissues, so the host's immune response plays an essential role in defense against microorganisms. Therefore, the severity of this disease is due to a variety of factors, including the presence of periodontopathic bacteria, high levels of proinflammatory mediators and low levels of anti-inflammatory mediators. This review attempts to enlighten the role of immune mechanisms involved in periodontal initiation and progression.

Keywords: Immunity; Health; Disease

Introduction

Periodontal disease is a multifactorial disease in which genetic, microbial, and environmental factors are involved. For the onset of periodontitis, many genetic loci participate in this process, which vary according to ethnic populations and may be influenced by environmental factors.

The term immunity is defined as resistance exhibited by the host against any foreign antigen including microorganisms. This resistance plays a major role in prevention of infectious diseases. The immune system is classified into the innate and adaptive system. The former includes cells of the myeloid line such as macrophages, neutrophils, natural killer cells (NK cells), and dendritic cells (DCs).

Innate immunity

It is the resistance which individual possesses by birth. It is by virtue of his genetic and constitutional make-up. It does not depend on prior contact with foreign antigen.

Adaptive immunity

The resistance acquired by an individual during life is known as acquired immunity or adaptive immunity.

Cells of the immune system

The principal cells of the immune system are derived from the lymphoid and myeloid arms of the hematopoietic system. In the bone marrow, the myeloid arm gives rise to peripheral dendritic cells (DCs), phagocytes (neutrophils and monocytes), mast cell precursors, basophils, eosinophils, platelets and erythrocytes. In the tissues, peripheral DCs, monocytes, and mast cell precursors further differentiate.

- **Mast cells:** They are major effectors of immediate hypersensitivity reactions. Mast cells are derived from the marrow; resides in most of the tissues very close to blood vessels. They contain cytoplasmic granules filled with effect or mediator molecules.
- **Basophils**: They are non-phagocytic cells and fight against foreign molecules or microorganisms by releasing their cytoplasmic granules which contain pharmacologically active components. They are mainly concerned with allergic responses.
- **Eosinophils**: They are primarily responsible for extra cellular killing of large parasites which cannot be phagocytosed. However, they also exhibit phagocytic activity to a smaller extent.
- **Dendritic cells**: They are the component cells of the innate immune system that are present in basal and supra-basal layer of oral mucosal epithelium. Dendritic cells participate in pathogenesis of periodontal disease by utilizing three mechanisms:
- Modulation of adaptive response,
- Direct interaction to the bacterial signals,
- Capability to influence other cells and ultimately the immune response.

DCs have been found to serve a role of surveillance by migrating in and out of oral mucosa under controlled by chemokines like Macrophage inhibitory protein - MIP-3α and MIP-3β and their receptors CCR6 and CCR7 respectively.

Macrophages

They are mononuclear phagocytic leucocytes, some of which are migratory and others are confined to tissues. Macrophage population in a particular tissue is maintained by three mechanisms:

- Influx of monocytes from circulating blood,
- Local proliferation and
- Biological turnover.

MHC and HLA systems

The Major Histocompatibility Complex (MHC) participates in the development of humoral and cell mediated immune responses. MHC molecules are a complex of surface glycoprotein molecules on which the antigens bind to for recognition by the T cell receptor. This function of the MHC molecule is also called -antigen presentation.

Neutrophils

They are active phagocytic cells and constitute the majority among. They are granular leucocytes possessing multilobed nucleus, primary azurophilic and secondary granules which stain with neutral dyes. The granules contain peroxidase, alkaline and acid phosphatases and defensins. They possess receptors for chemoattractant factors from microbes (e.g. Muramyl dipeptide or MPD) and complement components activated by microbes acting via Fc gamma - receptor binding to the Fc component of immunoglobulins (mainly IgG).

Lymphocytes

Interleukin-7 (IL-7) is a major factor in stimulating bone marrow stem cells to start down the path leading to the various lymphocytes (mostly B cells and T cells). Based on their function and cell membrane components (surface markers), Lymphocytes are of 3 types- T cells, B cells and Natural killer cells (NK cells).

Host-microbial interactions

The microbial biofilm that forms around the teeth is the main cause of periodontal disease initiation and progression.

- **Microbial response**: Biofilm is a complex community of microorganisms which produces various virulence factors that initiate the inflammatory response. The enzymes released by bacteria in the biofilm include proteases that are capable of disintegrating collagen, elastin, fibronectin, fibrin, and various other components of the intercellular matrix of both epithelial and connective tissue. Other proteases are leukotoxins which can kill leukocytes. Endotoxins are produced by Gram - negative bacteria which are strong inducers of cytokine production. The term lipopolysaccharide (LPS) is often used interchangeably with endotoxin. As the subgingival biofilm is majorly composed of Gram-negative bacteria, endotoxins produced by them leads to the induction of cytokine production by host cells, which causes inflammatory changes, like increased vascular permeability and engorgement of blood vessels. The role of bacteria in the initiation of gingivitis and periodontitis. Further investigations in this field led to the advancement in our knowledge of pathogenic bacteria causing disease progression. And it was found that specific Gram-negative, anaerobic, or microaerophilic bacteria were implicated in the causation of periodontitis. Most of the models of periodontal disease progression in the late 1980's stated that specific bacteria initiated the disease process by activating host responses, which were protective and destructive. The actual destruction of connective tissue and bone resulted primarily from inflammatory chemical mediators released by immunocompetent cells, such as matrix metalloproteinases, IL-1, and prostaglandins [3-9]. Löe., *et al*. (1986) [10] in their classic study of the natural history of periodontitis on tea plantation workers in Sri Lanka found that among individuals with poor oral hygiene and no access to dental care, some developed disease at a rapid rate, whereas others experienced little or no disease. In this study, it was appreciated that some unrecognized environmental factors or some individual differences in susceptibility to the disease were present in the population under study. During the same period, the importance of genetic variations in determining the development and severity of periodontal disease, with genetic influences accounting for as much as 30% to 60% of the variability in the clinical severity of periodontitis was established. Along with this, it was found that smoking and diabetes were powerful determinants of disease severity. These factors were considered as modifying factors for the outcome of the disease progression. So, to incorporate all these factors in the pathogenesis of the periodontal disease, non- linear model of disease progression was proposed [11-14]. Kornman in (2008) [15] have forwarded a biologic systems model of the pathogenesis of periodontal disease which incorporated the role of contributing factors in the pathogenesis diseases. According to this model, disease activity depends on an ecological shift in the plaque biofilm that can lead to the emergence of a specific set of microbial pathogens. Current understanding of host-microbial interactions.

Microbial insult

- **Host response**: The host immune response against microbial insult consists of innate and adaptive responses. The first defense against the invading periodontal pathogens and their products is junctional epithelium. The cells of the junctional epithelium have fewer desmosomes as compared to the normal epithelial cells, which account for its remarkable permeability. This permeability is closely related to the ingress of bacteria and their products and outward flow of the gingival fluid and transmigration of neutrophilic granulocytes between the epithelial cells. Because of this reason, junctional epithelium and the subjacent connective tissue becomes the battlefield for host-microbial interactions. The

cells involved in the first line of defense against many invading microorganisms are macrophages and neutrophils, which are important components of the innate immune response. However, these cells may not always eliminate infectious microorganism, and some pathogens may not be recognized by them. The adaptive immune response which is specifically directed against these organisms is then generated to eliminate them. Cells involved in the adaptive immune response are lymphocytes. Both innate and adaptive immune responses play a very important role in dealing with these infectious [16-18].

Initiation of host response by junctional epithelium

The junctional epithelium is constantly exposed to microbial flora which can initiate the inflammatory response. This inflammatory response is primarily mediated by neutrophils, which are the key components of the host defense against bacterial infection. Phagocytic macrophages then play an important role in the recognition of invading microorganism and to initiate the adaptive immune response.

Innate immune response

Gingival epithelium provides a physical barrier to infection and has an active role in innate host defense because the epithelial cells are in constant contact with the bacterial products [19]. α and ß defensins have an important role in the host immune response. Some investigations have shown that the primary role of ß-defensins may be to signal other innate and acquired immune responses, while LL37 and α-defensins may be more important for their antimicrobial properties in the gingival sulcus [20]. These peptides can activate the classical complement pathway and appear to upregulate IL-8 production by epithelial cells, which may enhance neutrophil recruitment to the site of infection [21].

Neutrophil response

Neutrophil are the primary cells involved in the initial immune response against invading microorganisms. It is well established that neutrophils are the most abundant type of leukocytes within periodontal tissues in acute and chronic periodontal lesions[22]. The neutrophil recruitment is along the gradient which is created by the pro-inflammatory cytokines, secreted in response to bacterial products. The most potent and abundant chemoattractant for neutrophils are CXC chemokines. The CXC chemokines are a unique family of cytokines, which participate in the regulation of angiogenesis. IL-8 is the most potent human CXC chemokine. IL-8 is secreted by various cells, including leukocytes, fibroblasts, endothelial cells, and keratinocytes, in response to both endogenous and exogenous stimuli[23]. In response to IL-8 secreted by the cells in the junctional epithelium, the neutrophils migrate along the chemoattractant gradient towards the surface of the junctional epithelium. The density of neutrophils within the junctional epithelium has been found to be increased towards more superficial layers of the epithelium, which are in close relationship with the subgingival plaque bacteria as compared to the deeper layers.

Role of Toll-like receptors (TLRs) in host microbial interaction

When microbes enter the tissue after penetrating the epithelial barrier, they are encountered by tissue macrophages, mast cells and immature dendritic cells. These cells must be able to distinguish between apoptotic particles generated by normal tissue turnover and particles that are indicative of infection. The molecules, mainly responsible for making this pivotal distinction are those of the family of pattern recognition receptors (PRRs). Mammals have several distinct classes of PRRs including Toll-like receptor (TLRs), RIG-I like receptors (RLRs), Nod-like receptors (NLRs), AIM2-like receptors (ALRs), C-type lectin receptors (CLRs), and intracellular DNA sensors such as cGAS. Among these, TLRs were the first to be identified, and are the best characterized. The family comprises 10 members (TLR1-TLR10) in human and 12 (TLR1-TLR9, TLR11 TLR13) in mice. Along with tissue macrophages, mast cells, and immature dendritic cells, these receptors are also expressed on lymphocytes, osteoclast precursors, osteoblasts, and stromal and epithelial cells, each of which has different toll-like-receptor expression profiles. Members of the TLR family are responsible for the recognition of pathogen associated molecular patterns (PAMPs), expressed by a wide spectrum of infectious agents; and self-derived molecules derived from damaged cells, referred as damage-associated molecular patterns (DAMPs). TLRs are largely classified into two subfamilies based on their localization, cell surface TLRs and intracellular TLRs. Cell surface TLRs include TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10, whereas intracellular TLRS are localized in the endosome and include TLR3, TLR7, TLR8, TLR9, TLR11, TLR12, and TLR13. The main effect of the stimulation of TLRs is the synthesis and secretion of pro-inflammatory cytokines and lipid mediators, thereby initiating the inflammatory response that recruits both soluble immune components and immune cells from the blood.

Adaptive immune response

The adaptive/acquired immune response is activated when the epithelial barrier, with its antimicrobial peptides and other components of innate systems, is breached. The pathogenic species present in the subgingival biofilm evade the anti-bacterial host defense mechanisms by releasing an array of virulence factors, which causes damage to the host tissue by immune/inflammatory interactions, which typically consist of neutrophils, monocytes/macrophages, dendritic cells (DCs). T-cells, and predominantly IgG-producing plasma cells.

- **T-cell activation in the adaptive immune response**: The T-cell adaptive immune response is activated by processing and presentation of bacterial antigens by lymphocytes, macrophages, and dendritic cells. After phagocytosis of bacteria, its recognizable surface antigens are presented on the surface of APC's.
- **Antigen presenting cells (APC's):** The APC's have the antigenic peptide with major histocompatibility complex (MHC) molecule located at their surface. Cytotoxic T-lymphocytes (CTL) expressing the CD8 co-receptor recognize the peptide

bound to MHC Class I molecules, whereas helper T-cells (Th) expressing the CD4 co-receptor does so with a peptide associated with MHC Class Il molecules. Co-stimulatory molecules such as B7-1 (CD80) and B7-2 (CD86) are also present on APC's that interact with CD28 on T-cells. Adhesion molecules such as ICAM-1 present on APC's are involved in the formation of strong immunological synapses to facilitate the proper activation of T-cells.

- **Interactions between APC's and T-cells:** There is a series of intracellular signaling cascade that is activated when a receptor is activated, which ultimately leads to the synthesis and secretion of biochemical mediators like cytokines, etc. The interface between lymphocytes and targets is termed 'immunological synapse' (IS).
- **T-cell receptor (TCR):** The TCR is a complex of integral membrane proteins that participate in the activation of T-cells in response to the presentation of antigen by APC's. MHC molecules on APC's that present antigen peptides to TCR complexes trigger TCR and induce a series of intracellular signalling cascades. Engagement of the TCR with APC's initiates positive and negative cascades that proliferation, differentiation, cytokine production, and/or activation-induced cell death. To mount an immunological response, the T-cell needs to receive a second signal from an antigen-presenting cell in the form of a co-stimulatory molecule. Co-stimulatory molecules act through different TCRs, such as the CD28 and TNFR families, producing a second signal that induces T-cell activation and proliferation.

Steps in the activation of T-cells

- Antigen which is phagocytosed by a macrophage is cleaved into polypeptides which are then transported to the surface for presentation to T-cells.
- The APC complex consists of both antigen and MHC. MHC complex is encoded by a group of genes, so different polypeptides are presented on the surface of the MHC which is responsible for diversity of antigen presentation. MHC presents only proteins which may be derived from foreign or self-proteins.
- Macrophage which is attached to the antigen, produces, produces IL-1 which activates CD4 cells.
- CD4 interacts with MHC Class-II on APC surface. This union is stabilized by other proteins LFA-1 on T-cells and ICAM 1 on APC.
- A co-stimulatory signal is formed by B7 protein on APC and CD28 and CD4 cells which results in the secretion of IL-2 by the helper T-cells and it is this step that is useful in the execution of all the functions i.e., regulator, effector, and memory functions. Production of IL-2 is the most crucial step in T-cells activation.
- **Cell-mediated immune response in periodontal diseases:** T-lymphocytes response to antigenic challenges is called as a cell-mediated immune response. T-lymphocytes can be functionally divides into CD4 (helper T-lymphocytes) cells and CD8 (cytotoxic T-lymphocytes) cells by the type of antigen receptor and some small numbers of accessory markers on their cell surface.
- **Helper T-cells (Th cells):** Helper T-cells are pivotal for the development of protective immune responses. The Th cells may belong to different cell lineages as they emerge from the thymus such as "natural" regulatory T (n Treg) cells and natural killer cells (NK-cells or they may demonstrate alternative patterns of differentiation of naïve CD4 T-cells. Thn cell is a T-cell that has differentiated in bone marrow, and successfully undergone the positive and negative processes of central selection in the thymus; When Thn cells are exposed to antigen by APC's, it results in the differentiation of Thn cells into Th0 cells. The Thn-cell proliferation proceeds mainly in four directions which are determined by the pattern of signals they receive during their initial interaction with antigen. The resultant four cell populations are Th1, Th2, Th17, and regulatory T-cells (Treg).
- **Th1 cell:** These cells mediate immune response against intracellular pathogens[32,33]. These are the main cells in generating an immune response against mycobacterial infections. Their main secretions of Th1 cells are IFN-y, lymphotoxin-a (LT-a), and IL-2. IFN-y is an important stimulator of macrophages for increasing their microbicidal activity.
- **Th2 cells:** These cells are involved in the generation of immune response against extracellular parasites including helminths. The Th2 cells get differentiated from Thn cells under the influence of IL-2 and IL-4. Th2 cells influence B-cells activation, proliferation, and immunoglobulin production. IL-10 produced by Th2 cells, suppress Th1 cells proliferation [34].
- **Th17 cells:** The Th17 cells represent a third effector arm of Cd4 T-cells and compliment the function of the Th1 and Th2 cell lineages. These play a critical role in the induction of tissue inflammation and tissue destruction that are hallmarks of many immune-inflammatory diseases. These cells mediate immune responses against extracellular bacteria and fungi [35].
- **Treg cells:** They play critical role in maintaining self-tolerance as well as in regulating immune responses. These cells get differentiated from Thn cells under the influence of TGF-B and IL-2.
- **Role of Th17 cells in periodontal diseases**: A distinct type of helper T-cell lineage, Th17 has been recently identified. This population secretes several pro-inflammatory cytokines, including the novel cytokine IL-17, and, hence, has been termed "Th17". The Th17 cell lineage is thought to play an important role in the pathogenesis of cell-mediated tissue damage

caused either by autoimmunity or immune responses against microbial infection. Th17 cells have been proposed to exert both pro- and anti-inflammatory functions. Further, these cells have also been shown to express higher levels of RANKL than Th1 cells [36].

- **Role of Regulatory T-cells in periodontal diseases:** Studies demonstrated that periodontitis patients showed an increased percentage of Treg cells in the gingival connective tissue as compared to gingivitis patients. It was concluded that Treg levels were upregulated in chronic periodontitis lesions as protection against self-antigens, such as collagen Type-1 [37] (Figure 1,2).

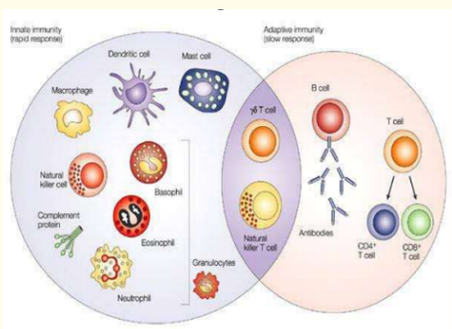

Figure 1: Cells of innate and acquired immunity.

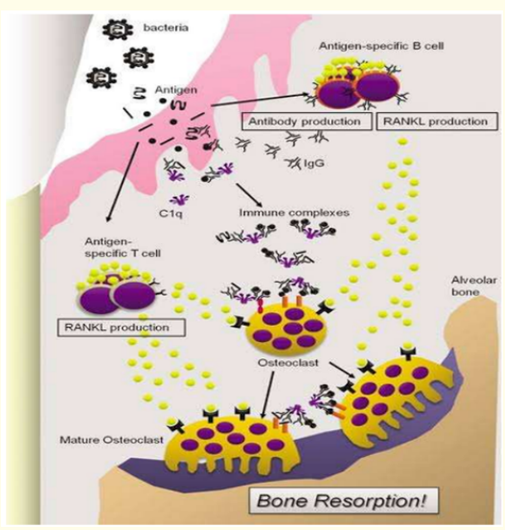

Figure 2: Host- Microbial Response.

Conclusion

There is sufficiently compelling evidence to conclude than immune reactions are indeed occurring in the affected tissues in destructive periodontal diseases. Principal lines of evidence that immune reactions are central to the pathogenesis of periodontitis are reviewed. Necessary components of immunologic reactions are present in gingiva in the periodontal disease. Differences between healthy and periodontitis patients with respect to some measures of immune function further indicate that immune reactions do occur in the gingiva during periodontitis. They are probably responsible for at least some of the destruction of connective tissue and bone that occurs. Mechanisms are more likely to be found in the pro-inflammatory and tissue-degrading effects of cytokines released in host-protective, antigen-specific and polyconal responses to oral bacterial constituents or products. Periodontitis increases in extent and severity across a large proportion of the human population with aging. These clinical changes are coincident with the host innate and adaptive immune-response systems recognizing the microbial transitions in the biofilms at sites of disease, resulting in altered levels of cellular and humoral immune effector cells and molecules reactive with various pathogenic microbial species.

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