Immunity of periodontal disease

Defenses against infection comprise a wide range of mechanical , chemical , and microbiologic barriers that prevent pathogens invading the cells and tissues of the body.

The commensal microflora (e.g. , in dental plaque) may also be important in providing protection against infection by pathogenic microorganisms through effective competition for resources and ecologic niches and also by stimulating protective immune responses. If these primary defenses are breached, then the cellular and molecular elements of the innate immune response are activated.

Innate immune response

Innate immunity refers to the elements of the immune response that are determined by inherited factors (and therefore “innate”), have limited specificity , and are “ fixed, ” in as much as they do not change or improve during an immune response .

Stimulation of innate immunity leads to a state of inflammation , and an important area of periodontal research is to understand the relationship between innate immunity and periodontal disease as a chronic inflammatory disorders.

If innate immune responses fail to eliminate infection (e.g. , in the

susceptible host), then the effector cells of adaptive immune response.

Barriers and molecules of innate immunity

I. Saliva

Role of saliva :

1. A vehicle for swallowing bacteria .

2. Inhibition of attachment of bacteria .

3. Bactericidal action by the peroxidase system.

4.Bactericidal action by lysozyme, lactoferrin and other Factors .

5. Saliva also contains specific immunoglobulin A (I gA) antibodies to periodontal pathogens that target specific antigens and inhibit bacterial adherence.

II. Gingival epithelium

Gingival epithelium has four functions:

1. Epithelial cells are tightly attached to each other.

2. Keratinization to resist trauma.

3 .Presence of permeability barriers.

4. Releasing molecules, such as IL-1 beta, capable of inducing or enhancing the local inflammatory reaction.

III. Gingival crevicular fluid

Gingival crevicular fluid functions are :

1.Washing non-adherent bacteria and their products out of the crevice.

2. Reducing the diffusion of plaque products into the tissues.

3. It also carries a steady supply of inflammatory protease inhibitors and host

defense agents such as complement and antibody, into the crevice.

IV. Complement system

The complement system is a part of the immune system that enhances the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, promotes inflammation, and attacks the pathogen's cell membrane. It is part of the innate immune system. The complement system consists of a number of small proteins found in the blood, synthesized by the liver, and circulate as inactive precursors. When stimulated by one of several triggers, proteases in the system cleave specific proteins to release cytokines and initiate an amplifying cascade of further cleavages.

The functions of complement are:

a. Chemotaxis cellular activation: Complement products released in this reaction attracts phagocytes to the site of infection e.g. C3a and C5

b. Opsonization: Once they arrive at the site of infection the complement components coat the bacterial surface and allow the phagocyte to recognize bacteria and there by facilitating the bacterial phagocytosis,e.g. C3b.

c. Cytolysis: Damage to the plasma membranes of the cells can lead to lysis of the cell by membrane attack complex.

Pathogen Recognition and Activation of Cellular Innate Responses

If plaque bacteria and their products penetrate the periodontal tissues, then specialized cell (macrophages and dendritic cells) of the immune system can recognize their presence by certain receptors and signal protective immune responses. These receptors called Toll like receptors(TLR) , TLRs are cell surface receptors that recognize pathogens,. Among the 11 human toll-like receptors identified so far, toll-like receptor-2 and toll-like receptor-4 are the most defined members involved in periodontal disease.

Pro inflammatory cytokines:

A number of cytokines are particularly important in innate immune signaling, The most important pro inflammatory cytokine is interleukin 1 beta (I L-1β), which exerts its action directly by:

1. stimulating the synthesis and secretion of other, secondary mediators such as prostaglandin E2 (PGE2) a potent vasodilator .
2. Up regulation migration of neutrophils in to the periodontium.
3. IL-1β also stimulates the secretion of the chemokine IL8, which stimulates neutrophil chemotaxis .

Cells of innate immunity

1. Neutrophils:

They are the initial leukocytes seen in the gingiva. They exit the circulation and migrate into the junctional epithelium and gingival crevice, where they provide the first cellular host mechanism to control periodontopathic bacteria. Polymorphonuclear neutrophils are short-lived cells, and also upon

interaction with pathogens and its toxins, they die in great numbers at acute inflammatory periodontal sites. Therefore, the accumulation and massive death of polymorph nuclear neutrophils are among major causes for tissue breakdown in progressive periodontitis.

Functions of Neutrophils

#Phagocytosis

Once they arrive at the site of inflammation, the phagocytes have to recognize the infectious agent. This can be enhanced if the organism has been coated by C3b or IgG (opsonization). Or they may attach to microorganism via their non-specific cell surface receptors. After attachment, the phagocytes proceed to engulf the micro-organism by extending pseudopodia around it.

2. Macrophages:

Macrophages develop from blood monocytes, which emigrate into the tissues from the blood and are triggered to develop into mature macrophages by cytokines.

Functions of macrophages includes:

1.Phagocytose and kill bacteria.

2.Remove damaged host tissue during inflammation

3. Trap and present antigens to lymphocytes for induction of immune responses.

Most of the above mentioned functions are carried out through the secretion of inflammatory mediators, including cytokines, prostaglandins, leukotrienes and complement components.

Adaptive Immunity

Adaptive immunity contrasts with innate immunity in the dynamic of the underlying cellular and molecular responses:

1. Adaptive immunity is slower.

2. Reliant on complex interactions between antigen -presenting cells and T- and B-lymphocytes.

3. Specificity of the responses .

4. The ability of adaptive immune responses to improve during exposure to antigen on subsequent infection events (memory).

Lymphocytes are the main cells of adaptive immune response:

I.T-lymphocytes or T-cells:

Derived from the thymus and play a role in cell-mediated immunity. Different types of T-cells include:

1.Helper inducer T-cells (TH-cells) or CD4:They aid in the immune response of the B-cells to differentiate into plasma cells and produce antibodies.

2. Cytotoxic T-cells or CD8: Stimulates cytotoxic and microbicidal activity of the immune cells.

3.T suppressor cell :down regulate or suppress immune response.

II.B-lymphocytes or B-cells:

Derived from liver, spleen and bone marrow. They are precursors for plasma cells and play a role in humoral immunity.

Activation of adaptive immunity:

Adaptive immunity initiates with antigen presenting cells (macrophage and dendritic cells) recognizing pathogen in the sites of infection and subsequently migrating in to the regional draining lymph nodes to present

the processed antigen peptides to naive T lymphocytes and induce their activation and differentiation in to effector cell s (helper or cytotoxic cells).

Immunity to dental plaque:

1.Cellular immunity to dental plaque

The cell-mediated response in periodontal diseases: It is so called because it involves contact between cytotoxic T-cells and antigen to be destroyed.

In adult periodontitis T helper- cells increase and T Suppressor -cells decrease with increased gingival inflammation.

2.The humoral response to plaque:

Afer immune reaction to antigens, most of the lymphocytes and plasma cells remain in the lymph nodes and secrete antibodies into the blood stream. The antibody predominantly is IgG, which can opsonize and activate the complement. These antibodies pass into the gingival inflammatory exudates and then out into the gingival crevice in the crevicular fluid.

Possible mechanisms of action of antibodies in periodontitis:

I. Binding to bacteria, Thus:

a. Opsonizing for phagocytosis.

c. Coating bacteria and inhibiting attachment.

d. Activating complement and thus enhancing opsonization.

Osteo- immunology in periodontal diseases:

As the advancing inflammatory front approaches the alveolar bone, osteoclastic bone resorption commences. This is a protective mechanism to prevent bacterial invasion of the bone, but it ultimately leads to tooth mobility and even tooth loss.

Histologic studies have confirmed that the bone resorbs so that there is always a width of non-infiltrated connective tissue of about 0.5 to 1.0 mm overlying the bone.

It has also been demonstrated that bone resorption ceases when there is at least a 2.5-mm distance between the site of bacteria in the pocket and the bone.

Osteoclasts are multinucleated cells formed from osteoclast progenitor cells. The key system for controlling bone turnover is the receptor activator of nuclear factor-κB (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) system.

RANKL is produced as a membrane-bound or secreted ligand by many cells. By activating its cognate **RANK receptor on the surface of pre-osteoclasts**, it triggers their fusion and differentiation into mature osteoclasts, thus activating bone resorption. The action of RANKL can be blocked by its soluble decoy receptor **osteoprotegerin (OPG),** by binding to RANKL, OPG prevents its further interaction with RANK, and subsequently all the down-stream molecular events that lead to osteoclast differentiation and bone resorption.

