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Periodontal Disease and immunity

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Abstract

The immune biology of periodontal disease continues to evolve, resulting in a number of foundational changes to the view of this disease across scientific disciplines. The first level of this evolution was fundamentally based upon the extraordinary microbiologic studies that provided a solid framework for understanding the basic stimuli for the disease.[1] more common periodontal diseases found in humans are gingivitis and periodontitis. These are inflammatory responses in the periodontal tissues induced by microorganisms in dental plaque, which may lead to tissue destruction.

The other concept is the interaction of the microorganism with the host which determines the course and extent of the resulting disease like gingivitis and periodontitis, as well as other less common periodontal diseases, which are chronic infectious diseases. Microorganisms may exert pathogenic effects directly by causing tissue destruction itself or indirectly by stimulating and modulating the host response. The host response is mediated by the microbial interaction and inherent characteristics of the host, including genetic factors that vary among individuals. In general, the host response functions in a protective capacity, preventing the local infection from progressing to a systemic, life-threatening infection. However, local alteration and destruction of host tissues, which is evident as periodontal disease, may result. Periodontal diseases represent the outcome of a complex interaction between

the host and the pathogenic microorganism in the unique environment of the tooth-to-tissue interface.[2]

Keywords: Localized Aggressive Periodontitis, Chronic Periodontitis, Immunity, Necrotizing Periodontal Diseases

Introduction

Immunity: Immunity is derived from Latin term meaning "free from".[3] Immunity is defined as "the resistance offered by the host to the harmful effect of pathogenic microbial infection ".It is the resistance exhibited by the host towards injury caused by microorganisms and their products or it is a reaction of body against any foreign antigens. The immune responses of mammals and the pathogenic/virulence capabilities of microorganisms have evolved together, each producing selective pressures on the other. Two primary attributes that are required by a pathogen for the production of disease are:

(i) The ability to metabolize and multiply in or upon host tissues; and

(ii) The ability resist host-defense mechanisms for a period of time sufficient to reach the numbers required to produce overt disease.

Many bacteria produce infection by multiplying primarily outside phagocytic cells and, generally, when they are ingested they are readily killed by the phagocytes. These microorganisms produce infection and disease only under two general circumstances:

(i) When the bacteria possess a structure or a mechanism that prevents them from being readily phagocytosed, and/or

(ii) When impairment exists within the host intracellular killing mechanisms. These types of bacteria may cause surface infections (mucosal surfaces), systemic infections or local infections.

(iii) Colonization and infection of a mucous membrane is very dependent on the adhesive properties of the bacteria.

The core elements of an immune system, and their essential functions.[3]

Types of Immunity

1. Nonspecific immunity/ innate immunity

2. Specific/ acquired immunity

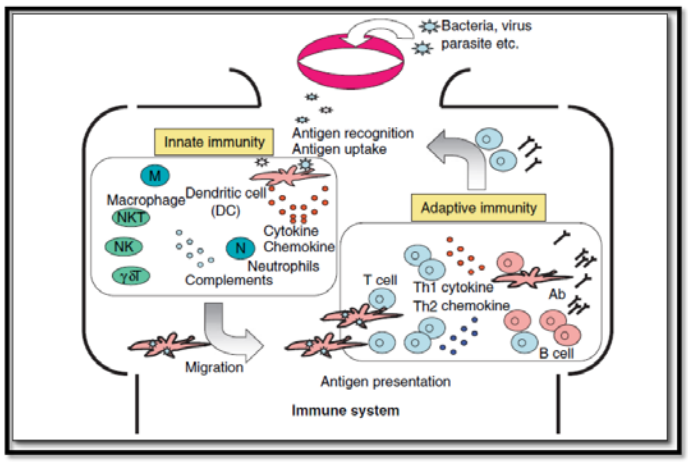

Fig. 1:Immune system - the immune system has two fundamental systems in response to invading microbes. Innate immunity is mediated by the release of inflammatory cytokines and chemokines, and by phagocytotic cells and killer cells. Adaptive immunity is mediated by the expansion of antigen-specific T and B cells. Both immune systems are well organized and interact with each other.

Innate Immunity

Innate immunity refers to any inborn resistance that is present the first time a pathogen has encountered.

The innate immune system solved the problems long ago, and vestiges of the original innate immune "battle plan" may be seen in all advanced life forms today. **Innate immunity: the science and its historical context**

1. The two aspects of innate immunity are the afferent (or sensing) arm-the afferent arm field deals with how all multicellular organisms perceive infection;

2. The efferent (or effector) arm- the efferent arm field with how we eradicate infection.

Each arm of innate immunity may further be divided into cellular and humoral components.

Acquired Immunity

It In contrast to innate immunity, there are other immune responses that are stimulated by exposure to infectious agents and increase in magnitude and defensive capabilities with each successive exposure to a particular microbe. Because this form of immunity develops as a response to infection and adapts to the infection, it is called adaptive immunity (also called specific or acquired immunity). The adaptive immune system recognizes and reacts to a large number of microbial and non microbial substances.The term adaptive immunity is usually reserved for that type of immunity that adjusts in order to respond to an invading microbe, i.e. it adapts. A synonym that has also been used is "acquired" immunity.[4]

Adaptive immunity carries with it the connotation of a heightened response to there-exposure to an antigen experienced previously. This we call immunological memory .Adaptive immunity, the clonal expansion of T and B cells by specific antigen, has dominated immunological research for decades.

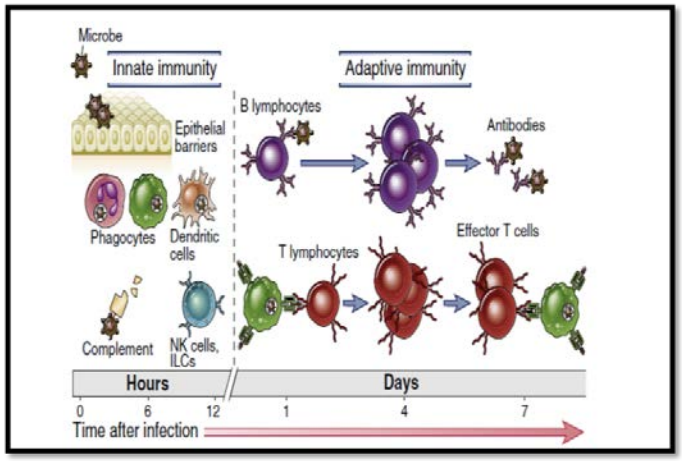

Fig.2: The mechanism of innate immunity provides the initial defense against infections. Adaptive immune response develops later and require the activation of lymphocytes. The kinetics of the innate and acquired responses is approximations and may vary in different infections.

Table 1: The differences between innate and acquired immunity

Property	Innate immune system	Adaptive immune system
Cells involved	Phagocytes(macrophages,neutrophils,dc's), Nk cells	T cells, b cells
Recognition receptors	Fixed in genome Rearrangement not necessary Limited diversity	Encoded in gene segments Rearrangement necessary High diversity
Ligand/antigens	Conserved molecular patterns (components of microorganisms)	Details of molecular structure (peptides,proteins,carbohydrates)
Development	Clonal (selected over evolutionary line)	Non clonal(selected in individual)
Response time	Immediate (0-4hrs)	Delayed (≈72hrs)
Site of response	Local , periphery	Secondary lymphoid tissues
Response	Production of inflammatory cytokines(IL-1,IL-6,TNF-α) and chemokines (IL-8) Induction of costimulatory molecules (CD-86,CD-40)	Clonal expansion or energy Production of effector cytokines(IFN-γ,IL-4)

Gingivitis

As inflammation of the gingiva increases, the transudate changes to an inflammatory exudate, which contains higher levels of serum derived molecules, vascular-derived cellular components of inflammation and locally derived molecules from the gingival tissues.as the

macromolecules derived from serum and from gingival tissues are structurally identical, it has been difficult to determine accurately the contribution of each to the exudate. However, there are clearly unique molecules that are produced in the local tissues.[5]

The most common form of gingivitis is plaque induced gingivitis. Common clinical findings in gingivitis include erythema, oedema, tissue enlargement, and bleeding. Two forms of plaque-induced gingivitis have been investigated: a naturally occurring gingivitis and experimental gingivitis. Neutrophils continue to dominate the junctional epithelium and gingival crevice with a marked increase in crevicular fluid flow. It is noteworthy that collagen loss in the involved tissues is evident in the earliest stages of gingivitis. Page and Schroeder report a predominance of plasma cells in the established lesion. Several studies of human experimental gingivitis have failed to demonstrate plasma cell dominance' however, increases in the proportions of plasma cells are evident with long-standing gingivitis. The host response to plaque bacteria is fundamentally an inflammatory response involving the processes described previously. Although gingivitis is not associated with loss of connective tissue attachment, it is evident histologically that some loss of collagen occurs within the connective tissues.[5]

Chronic Periodontitis

Gingivitis and periodontitis share the clinical feature of inflammation. In contrast, periodontitis involves clinically detectable levels of host tissue destruction that are not found in gingivitis. Alterations in the host response associated with specific periodontal pathogens are clearly evident. Increase in serum and crevicular fluid antibody specific to putative pathogens, including p. Gingivalis, aggregate bacteractinomycetom comitans, P. Intermedia, E. Corrodens, F. Nucleatum, and c. Rectus, are evident in patients with periodontitis.

Chronic periodontitis is characterized primarily as involving alternative pathway activation of complement, with C3 and B cleavage in gingival fluids observed. This suggests that even though pathogen specific antibodies are formed in chronic periodontitis, activation of the classical complement pathway by processes involving antibody-antigen binding does not predominate. MMP-8 is elevated in chronic periodontitis, whereas the levels of TIMP (TIMP-1) are not .the ability of the chymotrypsin-like enzyme of T. Denticola to activate MMPS may contribute to MMP-mediated tissue destruction at periodontitis sites with high levels of this microorganism. In addition, studies of GCF in chronic periodontitis reveal that collagenase activity is as much as six fold greater than that of gingivitis. Most of the collagenase activity associated with chronic periodontitis is due to the neutrophil collagenase MMP-8. Some microorganisms may modulate neutrophil secretion of collagenase. For example, the phagocytosis of F. Nucleatum and T. Denticola are associated with the release of high levels of elastase and mmp-8 from neutrophils. Clear evidence of variations exists among individuals in their susceptibility to periodontitis. Despite considerable accumulation of bacterial plaque including the presence of putative pathogens, some individuals appear to be resistant to the disease process whereas others develop disease. These differences relate primarily to variability in the host immune inflammatory response to the infectious challenge.[6]

Localized Aggressive Periodontitis

In aggressive periodontitis there is the evidence of phagocyte abnormalities and hyperresponsive monocytes/macrophages, leading to elevations in PGE2 and IL-1ß. Numerous mechanisms of serum-mediated bacterial killing are available, including lysis by the membrane attack complex of complement and

antimicrobial substances such as lysozyme. However, some bacteria, including all known strains of Aa as well as some strains of most putative periodontal pathogens, are resistant to serum mediated killing mechanisms. For serum-resistant bacteria, the neutrophil is the primary host response mechanism of bacterial control. Approximately 75% of patients with lap have dysfunctional neutrophils, involving a decreased expression of g-protein coupled receptors. The defect is evident as a decrease in the chemotactic response to several chemotactic agents, including the complement component 5a, N-formyl-methionyl leucyl phenylalanine (FMLP), and leukotriene B4. The defect is associated with a 40% deficiency in a 110-kilodalton membrane Glycoprotein, gp110, on the neutrophil surface.

In LAP the predominant collagenase found in tissues and crevicular fluid is MMP-1, and elevated levels of TIMP-1 is present. Patients with lap demonstrate elevated antibodies to A a. And antibody as well as complement is essential for opsonization and efficient phagocytosis. In lap the dominant serum antibody isotype IgG2 is specific for surface antigens of A a, including LPS and at least one major outer membrane protein. Some individuals possess a variant of the fc receptor on neutrophils (r131 allele of FcyrII-a) that does not efficiently bind IgG2, and this is one possible basis for disease susceptibility.it has been hypothesized that because this binding is less efficient, an antibody response more vigorous than normal is necessary to control the A a. Infection in LAP and that the progression in lap is limited by the development of a strong antibody response. In comparison, individuals with generalized aggressive periodontitis do not develop a strong antibody response, which supports the hypothesis that antibodies function to limit the disease process.[6]

Generalised Aggressive Periodontitis

GAP patients are frequently seronegative for A.a. or display low titers and avidity. Anti-A.a. Serotype polysaccharide IgG2, therefore, are considered to be protective against widespread AGP. Of importance are findings reporting antibody response to P. Gingivalis in gap forms. Patients suffering from these forms of disease frequently show both low levels of serum antibodies against P. Gingivalis and low levels of antibody avidity, indicating a specific inability of some gap patients to cope effectively with these bacteria.

Another important aspect of host response towards AGP microorganisms has been the recognition that PMNS of some lap and GAP patients present decreased migration and antibacterial functions. GAP patients have a decreased ability to mount high titers of specific IgG2 antibodies to A.a. These subjects exhibit a tendency towards progressive periodontal destruction leading to tooth loss over a relatively short period of time. LAP patients, on the other hand, seem to have better prognosis and do not express this trait. Since there are indications that at least some lap cases may progress into generalized forms, early detection of patients infected with A.a. But producing low levels of specific antibodies may allow early identification of a high-risk group for development of GAP. Serum antibody titers (IgG2 in particular) and/or avidity to A.a. May be particularly useful in the differential diagnosis of GAP and lap syndromes and in the early detection of the lap cases with high risk for progression into the more widespread forms of disease.[7]

Refractory Periodontitis

This group may represent a host defect of response to the bacteria. Sites in refractory patients with the highest total cytokine level demonstrated that refractory patients had higher IL-6 levels than stable patients. Moreover, the

presence of P. gingivalis, E. corrodens, or A.a only correlated with elevated GCF IL-1 levels.

Recent findings indicate that CD4/CD8 ratios are decreased in refractory periodontitis. P. Gingivalis LPS stimulation of monocytes cause a change in monocyte phenotype and increased IL-1β and pge_2 secretion serum from refractory patients demonstrates increased IgG antibody to multiple periodontopathogens. Recent studies to develop treatment modalities for these patients suggested altered host defenses, particularly cell-mediated, in patients with severe forms of periodontitis particularly that don't respond to treatment. Thus, the lack of response to treatment may result from impaired host defense or exaggerated inflammatory responses. Clearly additional studies are required to identify immune responses in these patients.[5]

Necrotizing Periodontal Disease

Increased cortisol levels have been associated with a depression of polymorpho nuclear leukocyte (PMN) and altered lymphocyte function. Lack of protective antibodies may be involved in the development of NUG. There is significantly higher IgG and IgM levels to an intermediate size spirochete and higher IgG levels to (P. Intermedia) in NUG. Lymphocyte function as measured by mitogenic response is severely depressed in NUG. It is apparent that regardless of the mechanisms involved, a general immune suppression (PMN function, antibody response, and lymphocyte mitogenesis) is associated with the onset of NUG.

Total leukocyte counts have been found to be similar for patients and controls. NG patients, however, displayed marked depression in polymorphonuclear leukocyte chemotaxis and phagocytosis as compared with control individuals. Reduced mitogen-induced proliferation of peripheral blood lymphocytes has also been found in ng patients. It was suggested that elevated blood steroids may account for the reduced chemotactic and phagocytic responses.[8]

Periodontal Abscess

In periodontitis, a periodontal abscess represents a period of active bone destruction (exacerbation), although such events also occur without abscess formation. The existence of tortuous pockets, with cul-de-sac, which eventually become isolated, may favors the formation of abscesses The marginal closure of a periodontal pocket, may lead to an extension of the infection into the surrounding periodontal tissues due to the pressure of the suppuration inside the closed pocket .Fibrin secretions, leading to the local accumulation of pus may favour the closure of the gingival margin to the tooth surface. Changes in the composition of the microflora, bacterial virulence, or in host defences could also make the pocket lumen inefficient to drain the increased suppuration.

In the development of a periodontal abscess, the first step may be the invasion of bacteria into the soft tissues surrounding the periodontal pocket, which will develop an inflammatory process through the chemotactic factors released by bacteria that attract inflammatory cells and lead to the destruction of the connective tissues, the encapsulation of the bacterial infection and the production of pus. Once the abscess is formed, the rate of destruction within the abscess will depend on the growth of bacteria inside the focus, their virulence and the local PH (an acidic environment will favor the activity of lysosomal enzymes).[9]

Conclusion

The role of the immune system in inflammation is the host response to injury or insult and a central feature of the majority of periodontal diseases. Innate immunity provides critical early phase defenses against invading microorganisms. Adaptive immunity, including the

development of the specific immune response, provides mechanisms by which the host can become more efficient in protecting against specific pathogens.

The immune system is well organized by a multitude of closely co-ordinated mechanisms. These include a multiple receptor and ligand complex for pathogen recognition, multifariously changing dendritic cells that induce immunity or tolerance, an array of co stimulatory molecules and cytokines that enhance or regulate the function of various immune cells, and several subsets of effector and regulatory T cells that have pathogenic or protective immune functions. All these mechanisms contribute to the infectious process and, although they are not yet fully understood, recent studies have provided important information for estimating the pathology and healing properties of periodontal diseases and for developing possible novel therapies.

The host-bacterial interaction theory may explain why otherwise healthy individuals with moderate levels of plaque do not exhibit loss of periodontal support. In these individuals, PMNs are effective in blocking invading pathogens without destroying the collagen content of the periodontium in the process. If these same pathogens attempted to invade the periodontium of people predisposed to periodontal disease, it appears that impaired chemotaxis and phagocytosis of defense cells may put these individuals at significantly greater risk for progressive periodontal destruction.[10]

In conclusion, there has been substantial progress is our understanding of the molecular mechanisms of host–bacteria interactions that result in the clinical presentation and outcomes of destructive periodontitis.The science has embarked from observations of variations in responses related to disease expression with a focus for utilization of the responses in diagnosis and therapeutic outcomes, to current investigations using cutting-edge fundamental biological processes to attempt to model the initiation and progression of soft- and hard-tissue destruction of the periodontium. As importantly, the next era in the immunobiology of periodontal disease will need to engage more sophisticated experimental designs for clinical studies to enable robust translation of basic biologic processes that are in action early in the transition from health to disease, those that stimulate microenvironmental changes that select for a more pathogenic microbial ecology and those that represent am rebalancing of the complex host responses and a resolution of inflammatory tissue destruction.

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