บทความปริทัศน์
Review Article

บทบาทของภูมิคุ้มกันต่อโรคปริทันต์
The Role of the Immune Response in Periodontal Diseases

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บทคัดย่อ

โรคปริทันต์เป็นโรคที่เกิดมาจากการสะสมของคราบจุลินทรีย์ การดำเนินโรคจะเป็นผลมาจากปัจจัยต่างๆ คือ ปัจจัยจากเชื้อจุลินทรีย์ ปัจจัยจากพื้นฐานทางพันธุกรรม และปัจจัยจากสิ่งแวดล้อม สภาวะและความสมดุลของปัจจัยต่างๆ เหล่านี้สำคัญต่อการพิจารณาสภาวะความรุนแรงของโรค ภูมิคุ้มกันของแต่ละบุคคลมีผลต่อความไวในการเกิดโรคของแต่ละบุคคลในกลุ่มประชากร ระบบที่ซับซ้อนของภูมิคุ้มกันมีผลต่อการดำเนินต่อของโรคปริทันต์หรือการหยุดยั้งของการเกิดโรค ความเข้าใจบทบาทของภูมิคุ้มกันที่มีต่อโรคปริทันต์จะนำไปสู่การป้องกันและรักษาโรคปริทันต์ที่เหมาะสม

คำไขรหัส: ภูมิคุ้มกัน โรคปริทันต์ การตอบสนองระบบภูมิคุ้มกัน การตอบสนองของร่างกาย

Abstract

Periodontal disease is known to be initiated by microbial plaque. The course of periodontal disease is affected by multiple factors such as microbial factors, genetic factors and environmental factors. The balance between these factors is important to determine the periodontal status and severity of the diseases. The host immunity is specific for each individual, resulting in the distinctive susceptibility of the disease in the population. Complex mechanisms of immunity could determine the progression or regression of periodontal disease. Understanding the role of immunity in perio-dontal disease could further lead to the proper management of the disease.

Key words: immunity, periodontal disease, immune response, host response

Introduction

Every species has its own immune response that develops by evolution. The more advanced the organisms evolve, the more complex the immune response will be. Immune response in the human being composes of the multiple mechanisms that mean to protect host from the foreign body and infection. Immune response functions with the range of specificity. It fights against many foreign bodies other than microorganisms including allergen that causes allergy. In addition, immune response functions to prevent and control the expansion and progression of cancer cells and altered self cells. The immunity must be regulated under a tight control to ensure proper functions. The redundancy mechanisms are formed and evolved to assist immune regulation.

The immune response can be classified into 2 types of the innate immunity and the adaptive immunity.[1]

1. The innate immunity

The innate immunity is the early protection against the microbial invasion. It composes of physical barriers, phagocytic cells, natural killer cells, and variety of molecules distributed in the vascular and secretory system. Innate immunity occurs immediately without complicated and delayed processing. The innate immune response operates through a cell-mediated response and the humoral response. The innate immunity has a rapid response that reduces the vast majority of invading microorganisms. Antimicriobial agents are produced and released into the vascular system and all secretion. These agents react non-specifically to the invading microorganisms. Innate immunity has many weapons against infection. Neutrophils and mononuclear phagocytes are the first line of defense against external infection by microorganism. Parasites are managed to be destroyed by eosinophils while cancer cells and altered self cells, from viral infection, are removed by natural killer lymphocytes. Successful invasion of micro-organisms through the natural barrier activates the removal of pathogens by the phagocytic cells. Phagocytes migrate to site of infection, are activated, engulf and destroy the invading microorganisms. Variety of chemical agents such as cytokines and chemokines are produced and released by the infected host cells and phagocytes. Phagocytes remove pathogens more efficiently with the help of opsonins such as antibody. Variety of toxic products are produced by the innate immune response including lysosomal enzymes, interferons, cytokines, complement proteins and acute phase proteins.

After an intense response of the innate immune system occurs, the adaptive immune response is further activated by varieties of chemical agents produced during interaction.

2. Adaptive (Acquired) immunity

The adaptive immune response is activated after the reaction of the innate immunity. The human adaptive immunity is a highly evolved mechanism. The immunity must recognize and interact with the foreign bodies with an ability to differentiate between the self molecules and the foreign molecules. The immune cells recognize and interact with the specific pathogens. The adaptive response has an ability to recognize and remember the specific pathogens that allows an intensive response during a repeated exposure of microorganisms. The adaptive immune responses are divided into two types of humoral immunity and cell-mediated immunity. T lymphocytes and B lymphocytes are the pivotal cells working in this pathway. T lymphocyte plays a central role in the adaptive immunity and also link the adaptive immunity with the innate immunity. The immune cells in the adaptive immune response recognize and response to the antigens that are presented by the major histocompatibility complex.[1]

The innate immune response and periodontal disease

The immunity in the oral cavity is processed in the similar fashion to that in any other part of the body. Periodontitis causes a destruction of the periodontal tissue which occurs in 5-10% of the adult population.[2] It is one of the most frequent bacterial infections found in the population. The course of periodontal disease is affected by the multiple factors including genetic factor, environmental factor (systemic and local factor) and microbial factor that interact among each others. The primary etiologic factor of periodontitis is the microbial plaque. The chronic inflammatory nature of periodontitis is the result from an interaction among a host response, an effect of bacterial toxicity and the environmental factors. The difference in the susceptibility of each individual in the population has been observed.[3,4] Some individuals are susceptible to periodontitis, resulting in severe destruction while others have an ability to resist periodontal destruction. Susceptibility of each individual is associated with the genetic background such as genetic polymorphisms of Fc receptors on phagocytic cells.[5,6]

In normal healthy host, neutrophils form a wall of protection between epithelium and microbial plaque to prevent bacterial invasion into the connective tissue layer.[7,8] Marshall RI 2004 stated that sulcular and junctional epithelium was the area that allowed antigen, cells and antibacterial agents to pass through.[9] These epithelium also produced antimicrobial agents such as β-defensins, cathelicidins and saposins.[9]

Polymorphonuclear leukocytes (neutrophils) are the cells that migrate to the site of infection at the early stage. The efficiency of bacterial removal by neutrophils is important to determine the course of periodontal disease.

In general, the proper function of host response should be able to fight against the microbial plaque and limit the progression of periodontal disease. However, a natural course of periodontal disease has been known as a cyclic pattern of disease progression and regression.[12] This could be attributed to the multiple factors.

The complicated niche of the microbial biofilm allows the periodontopathic bacteria especially *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans* and *Tannerella forsythia* to persist. These pathogens form the complex environment that supports and protects the pathogens from the destructive capability of phagocytes and the antimicrobial agents producing from the immune response. The ability to form biofilm and persist in the niche of these specific perio-dontopathic bacteria played an important role in initiation, progression and recurrence of periodontitis.[10,11,12,13]

The progression of periodontal destruction may be affected by the alteration of the host response. The persistence of the periodontal pathogens leads to the abnormal immune reactions that result in tissue destruction. A failure of phagocytes to remove pathogens causes these cells to be continuously activated. These frustrated phagocytes release the toxic products uncontrollably into the surrounding tissue resulting in the extensive destruction of the neighboring periodontal tissue.[14,15] Neutrophils produce variety of lysosomal enzymes that cause injury to the host cells such as fibroblasts, endothelial cells and keratinocytes when interacted with bacteria under a pathologic stage.[16] The severe destruction of periodontal tissue occurred in the aggressive periodontitis has been postulated to associate with a mass production of the toxic molecules and proinflammatory molecules such as arachidonic acid metabolites from neutrophils.[17,18,19,20] Cytokines with the proinflammatory roles including IL-1, IL-6, and TNF-α produced during the periodontal infection could induce bone

destruction.[21,22]

Cells functioned in the innate immune response such as neutrophils and macrophages produce a variety of cytokines that link and regulate many functions of the immunity. Neutrophils produce variety of cytokines such as IL-1 and IL-1 receptor antagonist.[23,24] Macrophages produce variety of proinflammatory cytokines such as IL-1, IL-6, IL-10, IL-12 and chemokines. Some of these cytokines are responsible for regulating T cell function and transmigration of monocytes, neutrophils and lymphocytes into the gingival tissue.[25] Schlegel Gomez R, *et al* (1995) showed the differentiation and activation stage of macrophage in the different stage of periodontal disease, which underscored the importance of macrophage in the local immune response in periodontal disease.[26]

The adaptive immune response and periodontal disease

Innate immunity works in accordance with the adaptive immunity. The adaptive immune response is crucial for inhibiting periodontal disease. Immunoglobulins prevent infections by many means including prevention of bacterial attachment, neutralization of the bacterial toxin, and opsonization of bacteria aiding phagocytosis. Non-protective antibodies are mostly found in the susceptible host and associated with the disease progression. The progression and regression of periodontitis was shown to be associated with properties of some B-cell clones.[24,27] Production of antibody that does not form specifically against virulent portion of bacteria has no beneficial. In this instance, an increase in the level of antibody does not always indicate the potential to remove bacteria. Different avidity of antibody to *P. gingivalis* was found in the different type of periodontal disease. Antibody with low avidity could result in the persistent response of the body. A clonal expansion of B-cells could also lead to a high production of IL-1 causing periodontal destruction.[28] Both quantity and quality of humoral response could affect the course of periodontitis.[29,30,31]

Antibody produced against periodontal pathogens is specific for each species. Antibody against *P. gingivalis* could reduce gingival inflammation in children whereas antibody to *A. actinomycetemcomitans* had no effect.[32] The difference in the ability of protection is specific for each individual which may be determined by a genetic trait.[12] IgG2 was found to be an important response against *P. gingivalis*. However, the specificity of Fc receptors in association with periodontal disease was not identified.[30,31,33,34]

Persistence infection induced the production of antibody that could kill bacteria and inhibited disease progression.[12] A late production of antibody in patients that had recurrent infection could function more effective against the same bacteria. For example, antibody produced against protease of *P. gingivalis* allowed C3 and IgG to opsonize *P. gingivalis* efficiently.[34,35] Recurrent infection of *A. actinomycetemcomitans* induced antibody against leukotoxin that could help protecting neutrophils from leukotoxin.[36]

An association of the innate immunity and the adaptive immunity in periodontal diseases

Cytokine production aids in the host protection under a controlled and balanced condition. Transmigration of leukocytes through tissue is dependent on the adhesion molecules on the endothelial cells. These molecules are presented with the induction of the specific proinflammatory cytokines and chemokines. These agents played a role in leukocyte selection including T-helper cells that involve in the inflammatory process.[37] Cytokines play a central

role in communication among cells in the immune system. The improper production of cytokine could lead to infection and progression of disease.[38] There is a complexity in the mechanisms controlling the cytokine production. However, genetic factor in sync with the environmental factors are believed to play a pivotal role in a proper control of the cytokine production. Offenbacher S, *et al* (1993) showed that host could be classified as a high and normal responder depended on the amount of inflammatory mediators and destructive-cytokine production.[39] High responders produced a large amount of toxic mediators in response to the microbial plaque that could result in a higher susceptibility to the disease than the normal responders. Hence, a progression of periodontal disease that continued and resulted in a loss of tooth could relate to the persistence of periodontal pathogens. This was associated with a high production of the proinflammatory cytokines such as matrix metalloproteinase and prostaglandin E2, and a low level of inflammation inhibitory cytokines such as IL-10, transforming growth factor β (TGF- β) and the tissue inhibitors of metalloproteinase.[40]

Cytokine polymorphisms have been identified and show the association with periodontal diseases. IL-1 polymorphisms such as IL-1 β +3954 together with smoking habits and the presence of IL-1 β และ IL-1 receptor antagonist (IL-1RA) were identified as risk factors for periodontal disease.[41,42,43] Other polymorphisms such as IL-1A +4845 และ IL-1B +3954 were also identified to associate with severity of periodontal disease in combination with smoking and were also claimed as the risk factors.[44]

Other than the destructive effects of cytokines, cytokines could also help to regulate the adaptive immune responses that associate with a progression of diseases.[22,45]

T lymphocytes play a central role in regulating human immunity. T cells are classified by the surface molecules as CD4+ T lymphocyte and CD8+ T lymphocytes. CD8+ cells or cytotoxic T cells (CTLs) function to detect and destroy foreign body, transplant tissue and viral infected cells. CTLs play an important role in the rejection of organ transplantation. They also have an ability to induce function of macrophages. CD4+ T cells or T-helper cells (Th Cells) play an important role in inducing B cells to plasma cells that produce antibody. T-helper cells could be subdivided into Th1 cells and Th2 cells that have a distinctive property in producing different set of cytokines.

A low response of the innate immunity and a failure to remove bacteria results in a low production of IL-12 which in turn reduce the activity of Th1 cells. In this instance, mast cells increased in the activity and released a large amount of IL-4 that consequently induced Th2 function. This further resulted in the activation of B-cells to produce antibody.[24,27,45] If infection could not be removed and B-cells were continuously activated and produced IL-1, the destruction of periodontal structure would continue.[24,27,45,46,47]

A balance of T lymphocytes subtypes including Th1 and Th2 could affect the status of periodontal disease.[24] Th1/Th2 response was affected by genetic polymorphisms that permitted the distinction in Th1/Th2 response of each individual. This could further result in the susceptibility of each individual.[48] The complex bacterial infection could shift the balance of Th1/Th2 response.[38]

CD8+ T cell has an effect on the equilibrium of Th1 and Th2 response.[49] In the study of CD8 clone cells, it was confirmed that CD8+ T cell could inhibit cells producing IFN-γ that allowed more activity of the humoral immune response.[49]

Th1 response produces IL-2 and IFN-γ ; whereas, Th2 response produces IL-4, IL-5, IL-6,

IL-10 และ IL-13. A reduction of Th1 response or and increase of Th2 response could result in an increase in periodontal destruction. A progression stage of periodontal disease was related to a high activity of Th2 cells producing IL-4 that could hinder cell-mediated response and increase humoral immunity.[50] B cells and plasma cells were confirmed to increase in numbers at the sites with periodontal destruction.[51,52,53,54] While a regression period was related to a high activity of Th1 response that produced IL-2 and IFN-γ.[50] IFN-γ increased the phagocytosis ability of neutrophils and macrophages that control the disease progression.[27]

Clonal expansion of B-cell and differentiation of B-cell to plasma cells need help from T-cells and cytokines. Even though the production of antibody is more dependent on the activity of Th2 cells, the equilibrium of both Th1 and Th2 cytokines determines the proper production of a high competent antibody. Yamamoto M, *et al* (1997) showed that gingival tissue of periodontitis patients have two profiles of cytokine production.[49] One group produced IFN-γ, IL-6, IL-10, and IL-13 while another group produced IFN-γ, IL-6, and IL-13. Most specimens did not show any trait of IL-2, IL-4 and IL-6. Cytokines productions that emphasized Th2 profiles resulted in the induction of B-cells in the diseased sites. The absent of IL-4 could lead to the accumulation of macrophage in the diseased sites.[49]

The innate immune response has a role in controlling the specificity and selection of the Th response. The production of IL-2 and IL-18 from monocytes and neutrophils assist the activity of Th1 response.[38]

Bacterial factors affecting the immune response in the periodontal diseases

The presence of pathogenic subgingival microflora alone does not cause the periodontal disease. The perfect components of bacterial plaque at the specific environment in the susceptible individual are required to initiate disease.[55]

Bacteria have evolved the mechanisms to evade host defense by producing virulence factors. These virulence factors function through variety of mechanisms to allow intrusion of bacteria and propagation of bacteria to the favorable target site. Toxic products produced from the periodontal pathogens can also contribute to the destruction of periodontal tissue directly. Variety of toxic substances produced and released by these periodontal pathogens are harmful to all components in the periodontal tissue. Most of periodontal pathogens produce proteases that have an ability to destroy the periodontal connective tissue and proteins involved in the immune response such as immunoglobulin and complements. The existence of the microbial plaque in untreated chronic periodontitis could lead to the intense production of proteases and other destructive enzymes from bacteria and host cells.[56]

P. gingivalis, A. actinomycetemcomitans, and spirochetes produce enzymes destroying collagen. Elastase-like enzymes were found to be produced from spirochetes and *Capnocytophaga* species.[57,58,59] Trypsin-like proteases and aminopeptidases were produced from *T. denticola* และ *Capnocytophago* species.[59,60,61] Dipeptidylpeptidases were produced from *P. gingivalis, P. intermedia* และ *Capnocytophaga* species.[59,62,63] Some bacteria also had fibrinolytic activity to digest hemoglobin.[64]

Basic inflammatory response which includes plasma proteinase cascade systems, clotting, and serum proteinase inhibitors (α1-proteinase inhibitor และ α2-macroglobulin) are also affected by the agents produced by the periodontal pathogens. *P. gingivalis* interfered with neutrophil migration by inhibiting the expression of E-selectin on endothelial cells and blocked the release of interleukin-8 (IL-8) from the epithelial cells. These activities inhibited the transmigration of neutrophils through epithelium.[65,66] *A. actinomycetemcomitans* could release toxic products that inhibited the function of neutrophils such as chemotaxis, hydrogen peroxide production.[67,68] *A. actinomycetemcomitans* could also produce leukotoxin that caused damage to neutrophils, monocytes and T lymphocytes.[69,70,71] Under continuous uncontrolled condition, these enzymes are harmful to the host tissue.

Critical issues

Currently, it is difficult to interpret and compare the data from the different studies. The complex immune biology together with the difference in the experimental setting hardens the ability to compare the results of each study. Differences in cell types used in the studies and the determination of the disease stage also confuse the interpretation of the result. More thorough experiments with standard setting should allow the better comparison of data.

Conclusion

Periodontal disease is the multifactorial disease. It is initiated by microbial plaque. However, host factors contributed through the immune response complicate the course of the periodontal disease. Even though many investigations showed an increase in the ability of the host response to control periodontal destruction with the recurrent infection, the persistence of periodontal disease is affected by multiple factors. The complexity of microbial plaque in the form of biofilm toughens the situation for the immune response to remove the periodontal pathogens.

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