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MICROBIAL DYSBIOSIS AND AUTOIMMUNITY IN PERIODONTAL DISEASE - A REVIEW

Periodontology

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ABSTRACT

Dysbiosis/infection and chronic inflammation could trigger autoimmunity by several mechanisms including bystander activation, dysregulation of toll-like receptors, amplification of autoimmunity by cytokines, epitope spreading, autoantigens complementarity, autoantigens overproduction, microbial translocation, molecular mimicry, superantigens, and activation or inhibition of receptors related to autoimmunity by microorganisms. The most prominent organisms involved in etiology of periodontitis are group of bacteria known as the "red complex," namely, Porphyromonasgingivalis, Treponemadenticola and Tannerella forsythia. Dysbiotic communities exhibit synergistic interactions that can enhance colonization, persistence, or virulence; bacteria known as keystone pathogens are involved in the breakdown of periodontal tissue homeostasis, whereas other, known as pathobionts, can trigger destructive inflammation once homeostasis is disrupted. The dysbiosis is closely related to periodontitis, and the relationship between the subgingivalmicrobiome and the immune and inflammatory response seems to be important in the pathogenesis of the disease. The microbiome-host interrelation is responsible for the occurrence of tissue damage in dysbiosis related infectious diseases. At systemic level, the link of autoimmunity and periodontopathogens needs to be interpreted from the role of dysbiosis in the occurrence of systemic autoimmune responses, related to the possibility of periodontopathic bacteria ability to generate an alteration of themicroflora in other organs with the consequent activation of autoimmunity mechanisms.

KEYWORDS

Dysbiosis, Autoimmunity, Bystander Activation, Auto Antibodies, Epigenetics

INTRODUCTION

The current paradigm of onset and progression of periodontitis includes oral dysbiosis directed by inflammophilic bacteria, leading to altered resolution of inflammation and lack of regulation of the inflammatory responses.. However, dysbiosis/infection and chronic inflammation could trigger autoimmunity by several mechanisms including bystander activation, dysregulation of toll-like receptors, amplification of autoimmunity by cytokines, epitope spreading, autoantigens complementarity, autoantigens overproduction, microbial translocation, molecular mimicry, superantigens, and activation or inhibition of receptors related to autoimmunity by microorganisms.The alteration in the activation of almost any immune process in a susceptible host could trigger immune dysregulation and autoimmunity.Immunodeficiencies in which the flaws are not in the effector response but in the immune regulatory mechanisms, have been called immune dysregulation disorders (1, 39).periodontitis as the result of dysbiosis of the oral microbiota guided by inflammophilic bacteria, leading to an altered resolution of inflammation and lack of regulation of the inflammatory responses (12).

Host- Microbiome Interaction

It has been observed in animals and humans with genetic predisposition, that the microbiota provides signals that induce antimicrobial effectors that are neutralized by inhibitory microbial signals, establishing as a result, a homeostatic relationship with the host (26). If a specific microorganism's line expands, this blocks the development of autoimmunity and improves their own chances of staying in that expanded state suppressing the host's adaptive and inflammatory responses (5)

Microbiome Dysbiosis

The change in the characteristic microorganism communities of a particular microenvironment is known as dysbiosis, also called dysbacteriosis. Bacterial translocation, related to the pathogenesis of multiple diseases, could be better described as atopobiosis, which is the appearance of microorganisms that are characteristic of a certain microenvironment in the "wrong" place.

It has been described that there are community members, specifically P. gingivalis (a suggested keystone pathogen in animal models), that even in low numbers can increase the virulence of the entire community (38); communication between it and normally commensal microorganisms (accessory pathogens) facilitate synergy and the transition to pathogenicity, allowing the continued development of the dysbiotic community and stimulating the inflammatory response.The virulence of the community rises as a consequence of the subversion of specific components of the immune response, and thus, this dysbiotic community increases causing additional damage and greater alteration to the homeostasis of the system, mediated mainly by pathobionts.

The most prominent organisms involved in etiology of periodontitis are group of bacteria known as the "red complex," namely, Porphyromonasgingivalis, Treponemadenticola and Tannerella forsythia.(33) However, culture-independent molecular methods used in recent metagenomic studies have revealed a more heterogeneous and diverse periodontitis-associated microbiota than previously known from cultural studies (10) Many of the newly recognized organisms (e.g., certain gram-positive bacteria and other species from the gram-negative genera Prevotella, Selenomonas, Desulfobulbus, Dialister and Synergistes) show as good or better a correlation with disease than the red complex bacteria (7)A recent metatranscriptomic study revealed that the majority of virulence factors that are upregulated in the microbiome of periodontitis patients is primarily derived from the previously underappreciated species that were not traditionally associated with periodontitis .(7) These recent human microbiome analyses and animal model- based mechanistic studies collectively suggest that the pathogenesis of periodontitis involves polymicrobial synergy and dysbiosis(20) The dysbiosis of the periodontal microbiota represents an alteration in the relative abundance or influence of individual components of the bacterial community (relative to their abundance or influence in health) leading to dysregulated host- microbial Review of Literature 15 crosstalk sufficient to induce destructive inflammation and bone loss. (13) .

Dysbiotic communities exhibit synergistic interactions that can enhance colonization, persistence, or virulence; bacteria known as keystone pathogens are involved in the breakdown of periodontal tissue homeostasis, whereas other, known as pathobionts, can trigger destructive inflammation once homeostasis is disrupted. Certaincommensals, though non-pathogenic by themselves intheoral environment, can promote keystone pathogen colonization and, as such, are implicated as accessory pathogens. P. gingivalis acts as a keystone pathogen at low colonization levels. Specifically, P. gingivalis induces the conversion from a symbiotic community structure to a dysbiotic one capable of causing destructive inflammation and periodontal bone loss. (6)

According to the polymicrobial synergy and dysbiosis (PSD) model, the host immune response is initially subverted by keystone pathogens with the help of accessory pathogens and is subsequently over-activated by pathobionts, leading to destructive inflammation in susceptible hosts. Therefore, according to the PSD model, periodontitis is not a bacterial infection in the classical sense (i.e., not caused by a single or a select few pathogens) but rather represents a polymicrobial community-induced perturbation of host homeostasis that leads to destructive inflammation in susceptible individuals

The dysbiosis is closely related to periodontitis, and the relationship between the subgingivalmicrobiome and the immune and

inflammatory response seems to be important in the pathogenesis of the disease. The microbiome-host interrelation is responsible for the occurrence of tissue damage in dysbiosis related infectious diseases.

Microbial Dependent Autoimmunity

The overproduction of autoantigens may well occur because the microorganisms produce enzymes that can break the extracellular matrix (i.e. fibrinogen, fibronectin, and type I collagen), creating "remnant epitopes" that act as autoantigens or because of an enzymatic modification of antigens (e.g. citrullination) that ends in the generation of autoantibodies (4).The post-translational modification of proteins by the enzymatic deamination of arginine residues converts positively charged peptidyl arginine to neutral peptidylcitrulline (28). This process is called citrullination and is catalyzed by the enzyme peptidylargininedeiminase (PAD) (37)

Microbial Translocation

In animal models, it has been shown that oral administration of P. gingivalis can induce intestinal dysbiosis (27) and result in endotoxemia and inflammation of the liver and adipose tissue, as well as an increase in the severity of collagen-induced arthritis mediated by an increase in T helper 17 cells (Th17) function at the intestinal level (16)

Molecular Mimicry

The oral cavity, especially in the presence of periodontal diseases, has proven to be a source of antigens both locally and systemically and molecular mimicry is undoubtedly one of the mechanisms by which it participates as a chronic infection in local and remote autoimmunity. The heat shock proteins (HSP) belong to a family of proteins conserved in prokaryotic and eukaryotic organisms during the evolutionary process, whose homology gives them a strong immunogenicity. In a chronic infection the immune response generated by human HSP60 and its bacterial equivalent, activates human vascular endothelial cells for the expression of E-selectin, intercellular adhesion molecule1, and the vascular cell adhesion molecule-1. This generates the activation of endothelial cells, smooth muscle cells, and monocytes/macrophages for the production of IL-6 and tumor necrosis factor-a (TNF-a) (40).

Superantigens

Microbial superantigens (SAg) induce the activation and expansion of a large number of T and B cells, which can result in the production of great amounts of regulatory and effector cytokines, modifying the host's immune functions (31). They are mainly secreted by gram-positive bacteria and are capable of inducing pathological symptoms (35). This SAg binding mechanism activates a large proportion of T cells (up to 25% of all T cells) in comparison to conventional antigens (0.0001% of all T cells) (30,34). SAg differs from regular antigens because interacts with the variable region of TCR-Vb chain and CMH-II in the antigen-presenting cell in a segment outside the antigenbinding site and induce the cell activation by cross linking of receptors . Therefore, SAg recognition by T cells has a significantly lower degree of specificity, as compared with their interaction with conventional antigens (36)

Bystander Activation

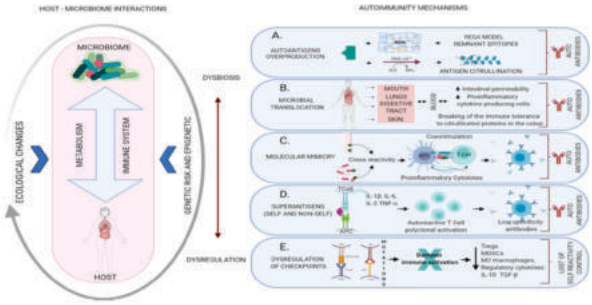
An adaptation mechanism of innate immunity has been described as bystander activation. This occurs as a consequence of infected cells which alert and give instructions to neighboring uninfected cells to produce inflammatory mediators either by direct cell to cell contact (mediated by GAP junctions by modulation of connexin) or by paracrine action (soluble signals). This mechanism may allow the immune system to overcome the pathogen's ability to disarm the immune signaling pathways in infected cells.

This mechanismcould participate in the pathogenesis of periodontitis from the activation of host responses to dysbiotic changes, which involve innate immunity, as in the case of dysregulation of TLRs and all the branches of immunity as in the hyperproduction of cytokines.

Dysregulation of TLRs

The activation of oral epithelial cells, cells of the innate and acquired immune response through CD14, TLR2, and TLR4, are considered a relevant event in the generation of the inflammatory response by the production of proinflammatory cytokines by binding with LPS of periodontopathic microorganisms in periodontal disease. The altered expression of these receptors has been reported in periodontitis (15, 2). TLR 1, 2, 3, 4, 5, 6, and 9 are differentially expressed in connective tissue and epithelium in periodontitis and in greater numbers in periodontitis patients compared to healthy tissue (2).

In periodontal disease, both IL-17 and IL-17F activate cells of innate immunity as neutrophils and cells from surrounding nonimmune tissues (fibroblasts and epithelial cells), by activating the transcription factor NF-kB. IL-17 can activate both fibroblasts and endothelial cells to increase secretion of IL-6 in the presence of TNF-a .

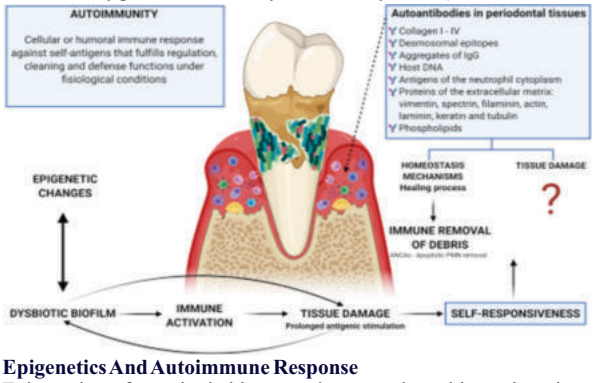


Epitope Spreading

There are 2 mechanisms for the epitope spreading to occur in autoimmunity, one independent of the antigenic presentation, in which inflammation and cytokine activation are sufficient to allow T cells to recognize cryptic epitopes and activate B cell complementarity (19), and the other dependent on binding to an APCs that occurs when there is no tissue destruction, and relies on processing and presentation to activate T cell which in turn reciprocally activate B cell (25)

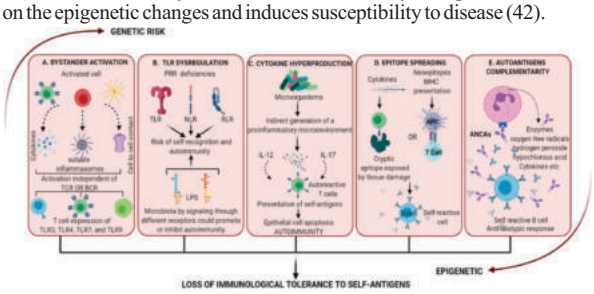
Autoantibodies In Autoimmune Damage

In periodontal disease, antibodies have been found against almost all types of collagen (I to IV), desmosomal epitopes, aggregates of IgG, host DNA, antigens of the neutrophil cytoplasm, proteins of the extracellular matrix (vimentin, spectrin, filaminin, actin, laminin, keratin, and tubulin) andphospholipids (32, 9, 18)prolonged antigenic stimulation caused by the rupture of the tissue and the release of the proteins of the extracellular matrix (a secondary event to the inflammatory process induced by microbial dysbiosis).



Epigenetics And Autoimmune Response

Epigenetics refers to heritable genomic expression without alterations in the original DNA sequence (42) leading to remodeling of the chromatin and activation or inactivation of a gene (23). There have been described three epigenetics modifications: DNA methylation, histone modifications, mainly by short-chain fatty acids and microRNA (miRNA) regulations (42).The post-translational modification of histone proteins in chromatin and the methylation of DNA are the two primary epigenetic mechanisms in periodontitis (42, 23). In addition, many environmental factors may have profound effects on the epigenetic changes and induces susceptibility to disease (42).



Conclusion

The translocation of oral microorganisms, its components or its

metabolites from periodontal tissues could be involved in the occurrence of autoimmune responses at a systemic level. Thus, at systemic level, the link of autoimmunity and periodontopathogens needs to be interpreted from the role of dysbiosis in the occurrence of systemic autoimmune responses, related to the possibility of periodontopathic bacteria ability to generate an alteration of themicroflora in other organs with the consequent activation of autoimmunity mechanisms.

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