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Original Research Paper

Periodontology

PERIODONTAL DISEASE AS LOCAL IMMUNE RESPONSE

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ABSTRACT Periodontitis is a complex inflammatory disorder which is caused by various causative factors playing a role simultaneously and their interaction with each other. One of the causative agents is pathogenic microbiota in the subgingival biofilm . The host is normally in a condition of homeostasis or symbiosis with the oral microbiome; nevertheless, homeostatic equilibrium can be disrupted due to an abnormal host response. This imbalance is caused by hyper- or hypo-responsiveness to inflammation, as well as a lack of adequate inflammation resolution, which is responsible for most of the disease's devastation. The innate immune response, constitutes a homeostatic system which is able to recognize invading microorganisms as non-self and launch an attack against them to eliminate them. Apart from innate immune response , adaptive immunity , particularly T-cells mediated immune response is highly dependent on antigen presenting cells, which after antigen capture undergo maturation and migrate towards lymph nodes where they produce distinct patterns of cytokines which will contribute to subsequent polarization and activation of specific T CD4+ lymphocytes. These cytokines are also correlated with extracellular matrix degradation and bone resorption through actions promoting secretion of matrix metalloproteinases and RANKL. All cytokines and inflammatory mediators have the ability to stimulate periodontal breakdown and collagen destruction , a characterization of progression of periodontitis . This article describe the involvement of host immune response in etiopathogenesis of periodontal disease.

KEYWORDS : Immune response; Pathogenesis ; Periodontal diseases; Cytokines; Matrix Metalloproteinase.

INTRODUCTION:

Periodontitis is a complex inflammatory disorder that develops over time. Periodontitis pathogenesis is a vexing subject for researchers. In the late 1980s and early 1990s, a pathogenic "red complex" was proposed as the most prominent explanation of periodontitis aetiology. Furthermore, fresh findings from metagenomic and metatranscriptomic investigations showed that, rather than one or several distinct pathogenic bacteria, a more complex microbial community is involved in the pathogenesis of periodontitis. However, more in-depth immunological study highlighted the critical significance of the local host immune response in periodontitis progression.

Periodontitis is caused by a number of aetiologic and risk factors, the most significant of which are the local microbiota and the immunological response of the host. The innate immune response is a homeostatic mechanism which recognize invading microbes as non-self and destroy them. Adaptive immune improves innate immune effector mechanisms by engaging an efficient loop for microbial clearance. Pattern Recognition Receptors that bind Pathogen-Associated Molecular Patterns initiate the innate immune system's first reaction to infections . The pattern recognition receptor and its downstream signalling are activated by contacts between the microbiome and all host cells, resulting in the initial wave of cytokine production . The interleukin-1 (IL-1), IL-6 and tumour necrosis factor are all examples of these cytokines. These cytokines are all pro-inflammatory cytokines with pleiotropic effects on lymphocyte promotion and tissue destruction.[1-2]

1. Etiology Of Periodontal Disease

Periodontitis is characterised by diverse subgingival microbial communities. The human body comprises a variety of ecosystems that provide a unique habitat for bacteria to colonise. Furthermore, there are multiple sites for microbial colonisation in the oral cavity. The periodontal sulcus/pocket, for example, is largely shielded from physical shear pressures in the oral cavity and includes the tooth root's hard and non-shedding surfaces, as well as the Gingival mucosa shedding surfaces in constant touch with gingival crevicular fluid. The epithelial surfaces are constantly renewed; yet, numerous of the most dangerous bacterial species are able to enter gingival tissues, surviving and escaping the immune system's attack. As a result, the subgingival environment has specific ecological characteristics and it is one of the most intriguing oral niches for evaluating the close relationship between oral microbial and immunological host response. Several bacterial species seen in the subgingival biofilm have been linked to diseased periodontal tissues and identified as possible pathogens. When Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, and Tannerella forsythia are present in sufficient quantities and in susceptible hosts, they are considered periodontal pathogens.[2]

2. Immune Response

A limited group of endogenous gram-negative periodontal bacteria causes periodontal disease by triggering immune responses. These processes cause the tissues surrounding and supporting the teeth to deteriorate, eventually leading to tissue, bone, and tooth loss. The innate immune system is physiologic reaction to a microbial threat by producing cytokines and chemokines with the help of recruitment of sufficient cells to infection sites. If the infection does not clear, the transition to the early lesion occurs, and the chronic lesion begins. Still, innate immune response pathways are triggered, which trigger the adaptive immune response. Innate immunity was formerly assumed to be nonspecific, characterised by macrophages and neutrophils phagocytosing and digesting bacteria and foreign substances. Surface receptors on phagocytes such as macrophages and neutrophils identify and bind bacteria's surface molecules. The toll-like receptors are example of pattern recognition receptors that discriminate between the

host and the bacterium. Chemokines are released once microbes and foreign substances are detected, attracting phagocytes. These toll-like receptors play a vital role in innate immunity and periodontal health maintenance. Overproduction of pro-inflammatory cytokines, on the other hand, may result in tissue damage.[3]

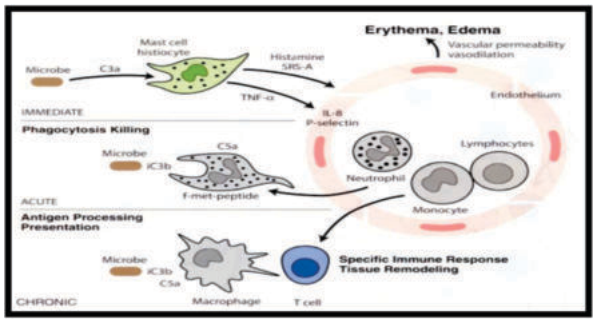

Figure 1: The natural history of inflammation actually starts before an irritant exists, with the transendothelial migration of resident leukocytes, especially the mast cell.[4]

Host Cells And Molecules Implicated In Periodontal Pathogenesis

Macrophages

Macrophages are mononuclear cells that orchestrate immune responses and play a role innate defence against microbes as well as specific immunity through their antigen-presenting activity. The different cytokines produced by macrophages can influence these responses.[5]

Natural killer cells

Natural killer cells are a kind of lymphocyte that plays a role in the innate immune system. They are important in the host's defence against infected and malignant cells because they recognize and kill them while also generating cytokines like TNF-α and interferon-g, which assist control other immune cells. Natural killer cell numbers rise dramatically from healthy gingiva to diseased periodontal tissues, indicating that they play a role in the immunological response to plaque buildup.[6]

T lymphocytes

T cells are mononuclear cells that are required for cell-mediated immunity. The two most prevalent kinds of T cells are helper and cytotoxic T cells, which are classified by their surface antigens and functional characteristics. Helper (CD4) T cells, primarily operate by multiplying and activating other lymphocytes such as B cells and other T cells, which are then actively implicated in the immune response to a pathogen . As the name indicates, cytotoxic (CD8) T cells are killers of target cells that display particular antigens on their surface. CD4 and CD8 T cells are seen in periodontitis lesions, and their ratio and relative numbers are considered to indicate the local immune response's regulatory state. Understanding T cells direct participation in periodontal bone resorption is one of the most intriguing new revelations concerning T cells and their contribution to periodontal pathogenesis.

The discovery of osteoprotegerin ligand, a molecule important for osteoclast formation as well as lymphocyte and lymph node growth and control, led to this knowledge. Periodontopathogen-activated T cells generate osteo protegerin ligand, which promotes the production of osteoclasts by binding to the nuclear factor kappa B receptor activator.

B cells

B cells are required for humoral immunity. When activated by the antigen , B cell pre-programmed to identify a specific antigen produces plasma cells that make specific antibodies. From health to periodontitis, the quantity of B cells increases. The fact that active periodontitis lesions have considerably greater B-cell levels implies that B-cell activation plays a role in disease development.[7]

Proinflammatory cytokines and lipid mediators

The enormous array of signalling molecules involved in the tissue's intricate cellular interactions can be classified as proinflammatory. The tissue response and the development of illness are often determined by the balance between them. The proinflammatory mediators listed below have been researched extensively in connection to periodontal disease aetiology.

Interleukin-1

The role of interleukin-1α and IL-1b in alveolar bone loss and periodontal disease has gotten a lot of attention. IL-1 is a strong activator of bone resorption and inhibitor of bone formation . IL-1 production by host cells can be stimulated by many periodontopathogens, and IL-1 levels are increased in diseased tissues.[8]

Tumour necrosis factor-α

TNF-α is a molecularly different cytokine with several biological functions similar to IL-1. Because of its propensity to induce bone resorption and other catabolic processes, TNF-α has been linked to periodontal disease.[9]

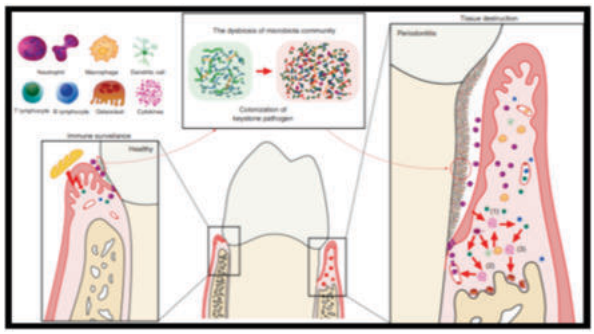

Figure 2: The homeostasis of periodontal tissue, pathogenesis of chronic periodontitis and roles of the involved cytokines.[9]

Role Of Neutrophils

Different chemo attractants, such as interleukin 8 (IL8), complement fragment C5a, or chemokine CXCL5, attract neutrophils to infection and inflammatory areas.

They make their way past the junctional epithelium and into the gingival sulcus and gingival crevicular fluid. Neutrophils in saliva retain their phagocytic activity as well as their capacity to produce ROS. There is generally minimal harm to the surrounding tissues if neutrophils and NETs do not proliferate excessively and are removed quickly. The major causes of tissue injury include the release of proteolytic and collagenolytic enzymes, as well as reactive oxygen species (ROS) inside host tissues, which typically result in extracellular matrix breakdown and chronic inflammation.

Connective tissue is normally destroyed to allow rapid transmigration of neutrophils and other cells involved in wound healing, but periodontitis results in a chronic inflammatory illness. As a result, the inflammatory response outweighs the resolution response, and host tissue damage progresses, eventually leading to pathological osteolysis and tooth loss.[10]

ROLE OF MMPS

The most widely reported MMPs in gingival crevicular fluid are MMP-8, MMP-9, and MMP-13 out of which MMP-8 accounts for 80% of the total collagenase that leads to periodontal tissue destruction.

Matrix metalloproteinases may also degrade non-matrix bioactive substrates such cytokines, chemokines and immunological mediators, allowing them to mediate both anti- and pro-inflammatory actions. As a result, matrix metalloproteinase levels should be considered not only as surrogate measures of tissue degradation, but also as part of a anti-inflammatory defence system.[11]

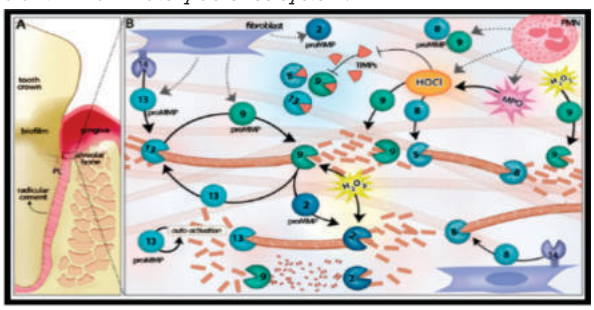

Figure 3 : Matrix metalloproteinase activation cascades in periodontitis[11]

Role Of Cytokines

Cytokines are important regulators of homeostasis and inflammatory processes, acting in the first wave of immune responses to pathogens. Immune surveillance and toleration of the local microbiota can be achieved without triggering a severe inflammatory response. However, after the colonization of a "keystone" pathogen, the microbiota's constituents and total counts are altered, elevating the pathogenicity of the entire community and disrupting tissue homeostasis. The immune response is over-activated under these circumstances, resulting in immune cell infiltration, osteoclastic activity stimulation, and final destruction of both soft and hard tissue.[12]

3. Destruction Of Periodontal Tissue

Destruction of bone

The disturbance of the equilibrium between osteoblast and osteoclast activity caused by bacterial products and cytokines is now widely recognised as one of the key mechanisms of inflammation-induced bone loss. The start of bone loss is linked to the toll-like receptor and inflammation-induced osteoclastogenesis pathway. RANKL can also be expressed by activated T-cells and B-cells.[13]

Destruction of extracellular matrix

Collagenases and other matrix metalloproteinases have been shown to play a key role in periodontal tissue degradation. Matrix metalloproteinases are clearly upregulated during periodontal inflammation. Tissue and plasma proteinases, as well as bacterial proteinases, are involved in matrix metalloproteinase activation, which is aided by oxidative stress. Various cytokines activate or inhibit the release of certain matrix metalloproteinases in periodontal disease. TNF-alpha, interleukin-1, and interleukin-6 are the major stimulatory cytokines for matrix metalloproteinases. Matrix metalloproteinase-8, which is mostly generated by neutrophils, is the most important collagen-degrading enzyme in periodontitis.[14]

4. Resolution of inflammation

Periodontitis is considered to be the outcome of uncontrolled inflammation. As a result, we should investigate the molecular and cellular processes of inflammation resolution in order to target them for treatment of periodontitis. Periodontal inflammation begins as a protective response to bacterial biofilm. In susceptible individuals, periodontal inflammation fails to resolve and chronic inflammation becomes the periodontal pathology. An essential goal of interventions in inflammatory disease is the return of tissue to homeostasis, defined as an absence of inflammation. Hence, the rapid and complete elimination of invading leukocytes from a lesion is the ideal outcome following an inflammatory event. Accordingly, inadequate resolution and failure to return tissue to homeostasis results in neutrophil-mediated destruction and chronic inflammation, with destruction of both extracellular matrix and bone.[15]

Lipoxins

Lipoxins are natural pro-resolving compounds derived from Aa and generated from endogenous fatty acids. Lipoxins have anti-inflammatory and pro-resolution dual properties. Lipoxins A4 and B4 were discovered to be inhibitors of PMN infiltration and stimulators of nonphlogistic macrophage recruitment when they were initially isolated.[16]

Resolvins

Endogenous lipid mediators called resolvins are produced during the resolution phase of inflammation. The necessary ω-3 polyunsaturated fatty acids obtained from the diet are used to make these lipid mediators. The two primary groups of the resolvin The E-series, which is produced from EPA, and the D-series, which is formed from DHA, have different chemical structures. The aspirin-modified COX-2 that converts EPA to 18R-hydroperoxyeicoapentaenoic acid and 18S-hydro peroxy eicoapentaenoic acid generates E-series resolvins in the vascular endothelium. Human monocytes quickly absorb neutrophils, which 5-lipoxygenase metabolizes into RvE1 and RvE2. Reduced neutrophil migration, phagocytosis of apoptotic cells and increased clearance of infection are all characteristic activities of resolvins, which help to stimulate tissue repair.

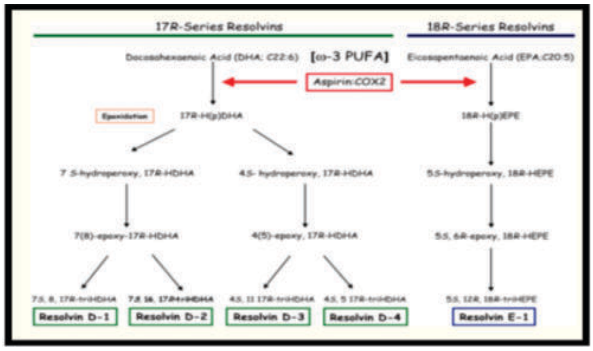

Figure 4 : Biosynthesis of resolvins.[17]

Omega-3

Polyunsaturated fatty acids have the most effective immunomodulatory properties of all the fatty acids. Omega-3 fatty acids are integrated into cell membrane phospholipids and act as precursors for lipid mediators that affect cell signalling and inflammation. This has anti-inflammatory properties. Furthermore, the metabolism of omega-3 fatty acids creates anti-inflammatory and immunoregulatory lipid mediators called "pro-resolving lipid mediators," such as resolvins and protectins, which limit immune cell passage and inhibit the synthesis of pro-inflammatory cytokines. Antibacterial activities are also seen in eicosapentaenoic acid and docosahexaenoic acid.[18]

Protectins

A lipoxygenase-mediated mechanism is also used to make protectins. DHA is transformed into a 17S-hydroxyperoxide-containing intermediate, which is taken up by leukocytes and turned into diHDHA, also known as protectins D1. Protectin D1 with a Th2 phenotype is produced by human peripheral blood lymphocytes, which reduces TNF and interferon production, blocks T-cell migration, and promotes T-cell death. Protectins inhibit PMN transmigration across endothelial cells and improve human macrophage clearance of apoptotic PMN.

Neutrophil apoptosis

Neutrophils are the first leukocytes to penetrate the inflammatory site and they have numerous methods for eliminating infections. Excess neutrophils, on the other hand, will extend the inflammatory process by continuing to generate antigens and secrete inflammatory cytokines, as well as harm tissue by secreting protein enzymes and toxic oxygen. As a result, timely neutrophil apoptosis and phagocytosis are critical for reducing inflammation and repairing tissue.[19]

Macrophage reprogramming

Macrophages have a self-renewal capacity similar to that of a stem cell and may multiply in the tissue once triggered by a stimulation. Macrophages show phenotypic variability due to their cellular differentiation, broad tissue distribution, and reactivity to numerous endogenous and external stimuli. M1 cells predominate from the start through the peak of inflammation or damage.M1 cells then participate in phagocytosis of apoptotic cells and pass the action to M2 cells as the process shifts to the resolution of inflammation and tissue healing. CD68 and major histocompatibility complex-II are surface markers on M1 cells, whereas CD163 and CD206 are on M2 cells.M1 cells produce more pro-inflammatory cytokines like TNF, iNOS, and others, whereas M2 cells release more immunoregulative cytokines like Arginase-1 and pro-healing cytokines like IL-10 and TGF-β.

Induction of pro-resolution mediators

Currently, a number of lipid mediators generated from polyunsaturated fatty acids are the most appealing pro-resolution mediators. Lipoxin, resolvin -D, resolvin -E, protectin, and maresin are some of them. Arachidonic acid, an omega-6 polyunsaturated fatty acid, is the source of lipoxins The capacity of lipoxins to inhibit neutrophil recruitment is the most widely understood mechanism implicated in their ability to resolve inflammation. lipoxins on the other hand, can increase macrophage phagocytosis of apoptotic neutrophils, which could lead to alternate macrophage activation.[20]

CONCLUSION

Microbial etiologic factors cause a range of host responses that promote inflammatory processes in periodontal disorders. Dysregulation of inflammatory and immunological pathways causes persistent inflammation, tissue damage, and disease in those who are vulnerable. Inflammation in the body is a well-coordinated network of cells, mediators, and tissues. It's critical to think about the immune response as an unit, rather than as a collection of individual modules. Because disease appears to be the outcome of a loss of control and a failure to return to homeostasis, a better knowledge of the molecular and cellular events that occur in this complex system is critical. The paradigm change in our knowledge of inflammatory disorders , such as periodontitis, is that inflammation resolution is an active process that activates particular biochemical resolution processes, rather than a passive one.[4] Precursor fatty-acid substrates and dietary supplies produce lipid mediators that inhibit proin flammatory signals.[18] Clinicians will need a precise map and molecular understanding of the resolution processes for inflammation and tissue injury in the future to care for periodontal infections and periodontal surgery patients. In the therapy of bacterially generated disease, a systematic temporal investigation of infection and resolution in human tissues is critical.

Increased inflammation and a failure of innate mucosal antibacterial mechanisms, according to studies of disease models, cause the infection to become chronic and the pathogen to remain. Uncontrolled resolution of the inflammatory process may thereby increase susceptibility to chronic inflammatory disorders.[20-21] Given the limited and ineffective therapy choices for periodontitis, study into the orchestration of this complex system might help us get closer to new treatment alternatives. Some medicines, such as selective cyclooxygenase 2 inhibitors and some lipoxygenase inhibitors, have found to be toxic to resolution programmes since many current and frequently used pharmaceuticals were created without awareness of their influence in resolution circuits. It will be crucial to see if resolution pharmacology leads to novel human disease therapies.[11-16]

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