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REVIEW ARTICLE

THE IMMUNOMODULATORY ROLE OF CYTOKINES IN THE PATHOGENESIS OF PERIODONTAL DISEASE

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Abstract

Background: Inflammatory periodontal diseases are one of the most acute problems of modern dentistry, which is associated with their widespread prevalence in the world. In the structure of periodontal diseases, periodontitis a leading place in the age group of 40-50 years. Many factors play a role in the etiology of periodontitis, the most important of which are the local microbiota and the host immune response. Cytokines play an extremely important role. Cytokines are key modulators of both homeostasis and inflammatory processes, acting in the first wave of responses against pathogens, stimuli at barrier sites and linking tissue cells to lymphocytes and additional cell populations.

Objective: The aim of the study was to analyze modern literature on the role of cytokines in the etiology and pathogenesis of inflammatory periodontal diseases.

Materials and methods: Data Extraction: A comprehensive electronic literature search was performed in the following databases:PubMed, Scopus,Web of Scienc, Google Scholar, EBSCO host from 2000 to 2024 terms: periodontitis, infection, inflammation, immunity, cytokines, interleukin.

124 articles were found and 50 full-text articles of high methodological quality were selected according to the review method used, the PRISMA.

*Inclusion criteria:*included clinical trials, considered randomized controlled trials, cross-sectional studies, case-control studies, and cohort studies in human subjects that evaluated the current literature on the periodontitis, infection, inflammation, immunity, cytokines, interleukin written in English articles.There was no limitation on minimal quality, minimal sample size, or the number of patients.

*Exclusion criteria were:*original primary studies, due to language limitations , abstracts, letters to the editor, book chapters, case reports, conference abstracts, duplicate publications, and in vitro and in vivo animal experimental studies.

Result: Many factors of general and local origin are involved in the development and progression of inflammatory periodontal diseases. Microorganisms and their products cause activation of the host immune system, which results in the release of cytokines and other proinflammatory biomarkers that cause tissue damage. The inflammatory process in periodontal tissues progresses through various stages, beginning with the infiltration of immune cells into the gingival tissue. Immune cells secrete proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α),which further promote inflammation and tissue destruction. The interaction between bacterial biofilm and the immune response, which is mainly controlled by cytokines, determines the course of periodontal disease.

Conclusion: The etiology and pathogenesis of periodontal disease is quite complex, diverse and not yet fully disclosed. Cytokines are control and modulate the immune response in periodontitis.

Keywords: periodontitis, infection, inflammation, immunity, cytokines, interleukin

Introduction

Inflammatory periodontal diseases are one of the most widespread diseases in the world. According to the report of the WHO scientific group, periodontal diseases in the group over 40 years old are 65-98%.[1]

The incidence of inflammatory periodontal diseases is growing, despite the advances in theoretical and practical dentistry. The medical and social significance of inflammatory periodontal diseases is determined by their prevalence among the population, premature loss of intact teeth, the

presence of foci of chronic infection in the oral cavity, which ultimately leads to a decrease in the quality of life of the population.[2]

Periodontitis is an inflammation of the periodontal tissues, characterized by progressive destruction of bone tissue. It is characterized by all the signs of inflammation (hyperemia, pain, swelling, dysfunction). These manifestations are based on disturbances in the barrier function of the periodontium and the immunological reactivity of the body.

Periodontitis is a polyetiological disease and its etiology is determined by both local and general factors.[4]Modern concepts the etiology and pathogenesis of periodontitis are based on two main factors: bacterial colonization and disruption of local and general immune mechanisms of the macroorganism.[5,6]

The latter may include sensitization of the macroorganism to antigens produced by certain types of pathogenic microorganisms.

Dental plaque bacteria initiate periodontal disease and trigger a chronic inflammatory reaction in periodontal tissues.[7] A number of microorganisms are capable of gradually producing various pro- and anti-inflammatory cytokines in cells. Their excessive production during chronic inflammation can have pathological consequences in periodontitis.[8]

After colonization, the microbiota and their total number are altered and tissue homeostasis is disrupted i the immune response is over-activated, leading to immune cell infiltration, activation of osteoclastic activity and ultimately to the destruction of both soft and hard tissues.[9] In the pathogenesis of periodontitis, cellular mediators of immune reactions (cytokines) play a significant role in regulating the immune response.[10]

In first the term cytokine (Greek-cyto, cell, and-kinos, movement) was coined by Stanley Cohen in 1974 and refers to peptides, proteins, and glycoproteins that play a role in controlling cell survival/death, growth, differentiation, and effector functions in tissues and immune cells.[11,12]

Cytokines also participate in alerting the body through the nervous system that an infection is underway, by causing pain or discomfort.[13]

Cytokines are small, low molecular weight, non-structural proteins, the cytokine molecules include interleukins, interferon, growth factors, cytotoxic factors, activating and inhibiting factors, colony stimulating factors.[14] Cytokines are important molecules for cell communication.and intercrines that have complex organizational effects on inflammation and immunity (figure 1.).

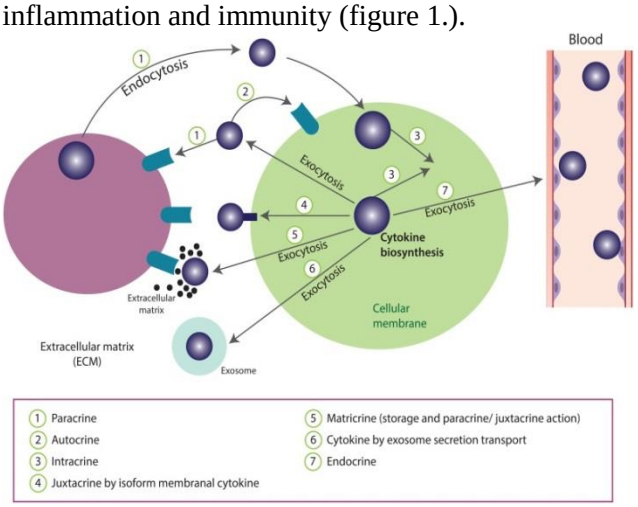

Figure1. Basic mechanisms of cell communication.

Cytokines have exceptional biological activity.[15] There are three functional categories of cytokines:

- cytokines that regulate innate immune response,
- cytokines that regulate adaptive immune response
- cytokines that stimulate haematopoiesis.

The biological activity of cytokines is mediated by specific membrane receptors that can be expressed on virtually all cell types. A cytokine causes a conformational change in multiple receptors, which leads to activation in the intracellular elements associated with the receptor, and a signal is transmitted to trigger subsequent intracellular events (figure 2).[16]

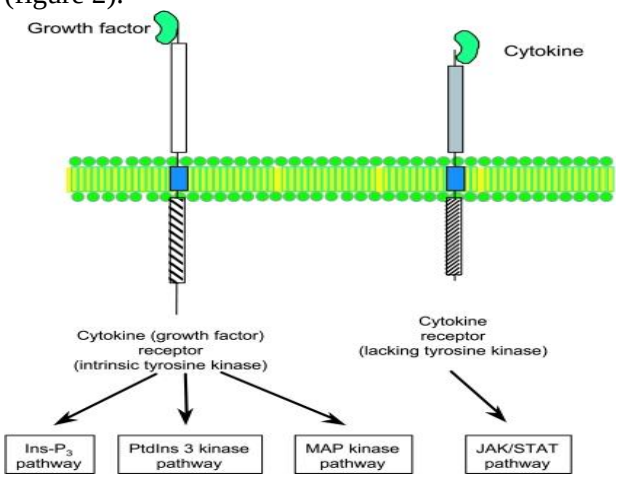

Figure2.Model of signal transduction from cytokine cell surface receptors with either

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intrinsic protein kinase activity (classical growth factors), or lacking protein kinase activity (inflammatory cytokines). InsP3 = inositol 1,4,5-trisphosphate; PtdIns 3-kinase = phosphatidyl inositol 3-kinase; MAP kinase = mitogen-activated protein kinase; JAK-STAT = Janus kinases and signal transducers and activators of transcription.

Most cytokines are not produced exclusively by one specific cell type. There are several options for classifying cytokines depending on the principle underlying them. Mediators can be systematized: a) by structure; b) by biochemical and biological properties; c) by the types of receptors through which they perform their biological functions; d) depending on the type of immune system cells producing these proteins (interleukins, mono- and lymphokines).[17] Moreover, some cytokines are produced by both immune and non-immune cells. In general, cytokines are most important in the regulatory processes of the immune system and can be classified into 5 subgroups based on their biological action(figure 2):[18]

- Interleukins (IL1–IL18) are secretory regulatory proteins that provide mediator interactions in the immune system and its connection with other body systems.
- Interferons (IFN-α, -β, -γ) are antiviral cytokines with pronounced immunoregulatory action.
- Tumor necrosis factors (TNF-α, -β) are cytokines with cytotoxic and regulatory actions.
- Colony-stimulating factors (G-CSF, M-CSF, GM-CSF) are stimulators of growth and differentiation of hematopoietic cells, regulating hematopoiesis.
- Chemokines (IL8, IL16) are chemoattractants for leukocytes.

Moreover, some cytokines are produced by both immune and non-immune cells.
In general, cytokines are most important in the regulatory processes of the immune system and can be classified into 5 subgroups based on their biological action(figure 3).[18]

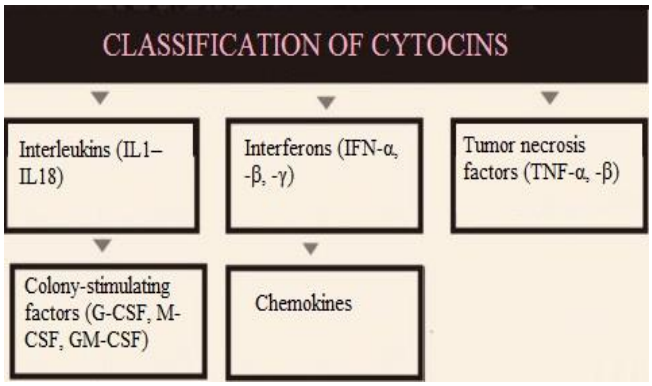

Figure 3. Classification Cytocins

Growth factors are regulators of growth, differentiation and functional activity of cells of various tissue origins (fibroblast growth factor, endothelial cell growth factor, epidermal growth factor) and transforming growth factors (TGF-β). Cytocins also categorized according to the structural homology of their receptors as class I or class II cytokines.[19]In addition, cytokines are often classified according to their functional ability to contribute to inflammation into proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-12, IL-18, and IFNγ or anti-inflammatory cytokines, such as IL-4, IL-10, IL-13, and TGF-β.[20]The well-established pro-inflammatory cytokines (members of the IL-1, IL-6 and TNF families) are reviewed first.[21] The related receptors, downstream signalling pathways and functions of these cytokines are summarized in fig 4.

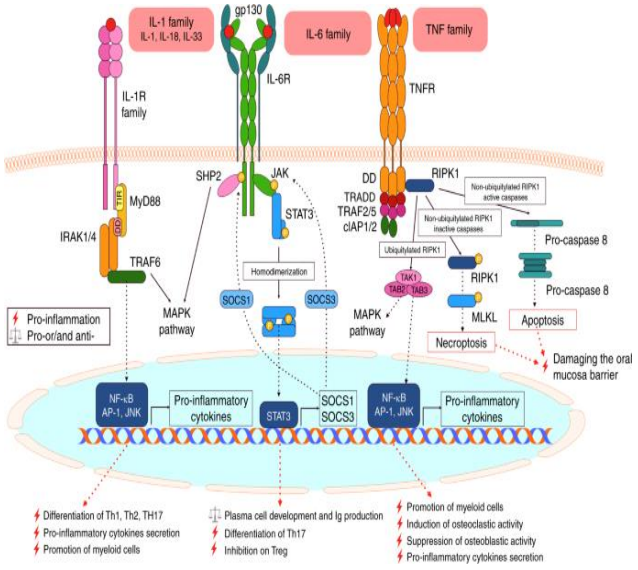

Fig.4 Pro-inflammatory cytokines, related receptor complexes and downstream signalling

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pathways. Most IL-1 (represented by IL-1, IL-18 and IL-33), IL-6 and TNF family members have pleiotropic effects on lymphocyte promotion and tissue destruction and act as pro-inflammatory cytokines. By binding to their corresponding receptor, IL-1 family members mainly activate transcription factors related to T cell activation and pro-inflammatory cytokine secretion, and IL-6 mainly mediates B cell activation. Depending on the state of key transduction proteins, the binding between TNF family members and their related receptors can lead to very different cell fates that include death (apoptosis and necroptosis) or life (secretion of pro-inflammatory and osteoclastogenic factors) and both lead to the destruction of periodontal tissue.

Disruption of their synthesis, production and reception underlies many immunopathological processes, including periodontitis.[22,23]

Recent studies in the field of cellular and molecular biology have provided a better understanding of the mechanisms of inflammatory and immune responses in periodontitis. It has been shown that at the onset of the inflammatory process, inflammatory mediators - cytokines such as interleukin-1, tumor necrosis factor-alpha and interferon-gamma play an important role. These cytokines also regulate bone resorption activity and are present in affected periodontal tissues. It has also been shown that metalloproteinases, which destroy the extracellular matrix, have increased activity in affected areas, and increased levels of their inhibitors correlate with the absence of disease activity.[24]

The spectrum of their action is activating, including a cascade of immunopathological reactions: activation of the lymphocytic link of immunity, proliferation and differentiation of T- and B-lymphocytes, increased cytotoxicity, production of immunoglobulins, increased functional activity of neutrophils, osteoclasts, fibroblasts, increased phagocytosis, bone resorption and activation of fibroplastic processes.[25]

One of the most important components of the cytokine response are Toll-Like Receptors (TLRs), which play a role in the primary detection of microorganisms on the oral mucosa. Their activation leads to the production of a cascade of cytokines, many of which directly or indirectly stimulate the formation of osteoclasts.[26]

Pro-inflammatory cytokines such as IL-1, -6, -11 and -17, TNF and oncostatin M, Kinins including bradykinin, thrombin and interferon-beta (IFN-b) and gamma (IFN-g) that reduce bone regeneration.[27]

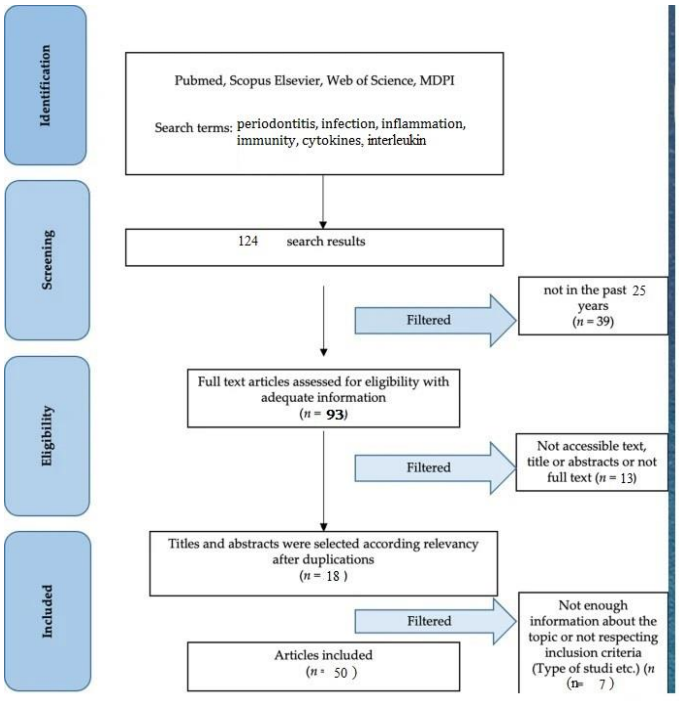
The effects of all cytokines depend on the microenvironment, target cells, interaction with synergistic or antagonistic cytokines with cytokine inhibitors. A special role is given to proinflammatory cytokines, which play a key role in the development of immunopathology in periodontitis, the development of inflammatory and destructive processes. At the same time, the multiplicity of functions of cytokines can also be important in the regulation of reparative processes in the body, including osteogenesis.[28]

This review, we have focused on an up-to-date of the pathogenesis of periodontal disease and the role of cytokines in periodontal disease.

Materials and methods

Data Extraction: A comprehensive electronic literature search was performed in the following databases:PubMed, Scopus и Web of Scienc,Google Scholar, EBSCO host from 2000 to 2024 terms: periodontit biofilm, oral microbiome, etiology and pathogenesis of inflammatory periodontal diseases new treatments, 124 articles were found and 50 full-text articles of high methodological quality were selected. The selection of articles is demonstrated in the PRISMA flow chart (tabl.1).

Table.1 PRISMA flow chart selection of articles



Inclusion criteria:included clinical trials, considered randomized controlled trials, cross-sectional studies,

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case-control studies, and cohort studies in human subjects that evaluated the current literature on the periodontitis, infection, inflammation, immunity, cytokines, interleukin written in English articles.
There was no limitation on minimal quality, minimal sample size, or the number of patients.
Exclusion criteria were: original primary studies, due to language limitations, abstracts, letters to the editor, book chapters, case reports, conference abstracts, duplicate publications, and in vitro and in vivo animal experimental studies.
Results. Many factors of general and local origin are involved in the development and progression of inflammatory periodontal diseases. Microorganisms and their products cause activation of the host immune system, which results in the release of cytokines and other proinflammatory biomarkers that cause tissue damage. The inflammatory process in periodontal tissues progresses through various stages, beginning with the infiltration of immune cells into the gingival tissue.
Primary parodontoid tissue injury is a reaction of resident leukocytes and endothelial cells to bacterial biofilm. At this stage, there are no signs of clinical inflammation, but tissue changes can be observed histologically. Bacterial metabolic products trigger junctional epithelial cells to produce cytokines and stimulate neutrons to produce neuropeptides, which cause vasodilation of local blood vessels. Neutrophils leave the vessel and migrate to the site of inflammation in response to chemokines. Early injury follows with an increase in neutrophils in the connective tissue and the appearance of macrophages, lymphocytes, plasma cells, and mast cells. Complement proteins are activated. The epithelium proliferates. Fluid flow in the gingival sulcus increases. Next stage Macrophages, plasma cells, T and B lymphocytes dominate, and IgG1 and IgG3 B lymphocyte subclasses are also present. Blood flow is impaired, collagenolytic activity increases, and collagen production by fibroblasts increases. Clinically, this stage is moderate to severe gingivitis with bleeding gums and changes in color and contour. The final stage is the transition to periodontitis: a progressive lesion. Histologically and clinically, irreversible attachment loss and bone loss are observed. The inflammatory lesion extends deeper, affecting the alveolar bone.
Immune cells secrete proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), which further promote inflammation and tissue destruction. The effects of all cytokines depend on the microenvironment, target cells, interaction with synergistic or antagonistic cytokines with cytokine inhibitors. A special role is given to the so-called proinflammatory cytokines, which play a key role in the development of immunopathology in periodontitis, the development of inflammatory and destructive processes (fig. 5).

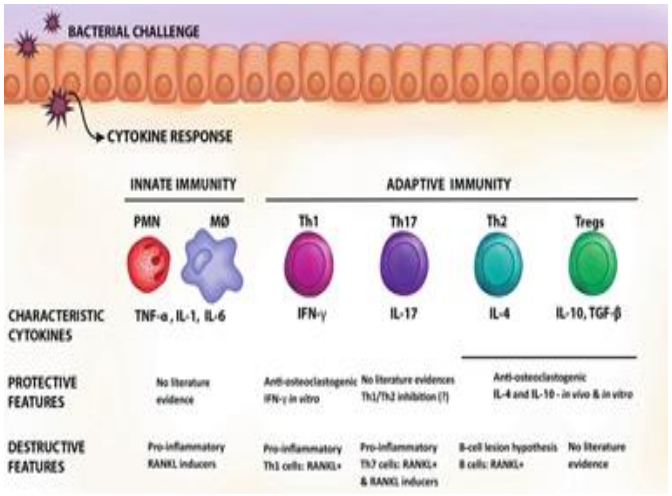

Fig.5 Cytocines and Periodonta Disease

The interaction between bacterial biofilm and the immune response, which is mainly controlled by cytokines, determines the course of periodontal disease.

Discussion

Research into the mechanisms of the immune response involved in gum disease has advanced in the last few decades. The immediate response to bacterial infection involves a non-specific immune response that results in the synthesis of several cytokines and other mediators.[29-34]
This "inflammatory attack" on the gum tissue destroys connective tissue and alveolar bone, which is the hallmark of gum disease.[35]
Today, there is clear evidence that both innate and acquired immune responses are involved in the pathological process of periodontitis. The local reaction to a bacterial infection activates innate immunity, producing a large number of cytokines and inflammatory mediators that lead to the destruction of connective tissue and the alveolar process of the jaw, indicating the development of periodontitis.[36]
Inflammation develops 2-4 days after plaque accumulation in the gingival sulcus. At this stage,

hydrostatic pressure in the microcirculatory bed increases, which leads to increased vascular permeability.[37]

Since the effect of microorganisms persists, the inflammatory response continues to increase, leukocyte infiltration of connective tissue increases, and collagen fibers are severely destroyed. The periodontal pocket deepens due to the growth of biofilm in an anaerobic environment. This process leads to damage to periodontal tissues.[38,39]

It is assumed that the development of the disease is associated with a combination of several factors: the presence of periodontopathogenic microorganisms, a high level of proinflammatory cytokines, matrix metalloproteinases (MMP), and a low level of IL-10.[40]

According to this concept, the balance of cytokines determines whether periodontal tissue destruction occurs or homeostasis is maintained. The role of periodontopathogenic microorganisms in determining the progression of this disease is very complex. Periodontitis is not associated with the presence of one specific microorganism, but includes a wide range of periodontopathogens. Numerous studies related to the study of the composition of biofilm in patients with periodontitis have shown that periodontal diseases are associated with a higher content of anaerobic gram-negative microorganisms, such as Prevotella, Leptotrichia, Veillonella, Porfiromonas, Treponema. These microorganisms destroy periodontal tissues directly through pathogenic products such as endotoxins, collagenases, causing an immune response.[41]

Thus, the degree of damage to periodontal tissues depends on the ratio of the strength of damaging factors and the level of protective and adaptive mechanisms, that is, the resistance of this organism, where one of the main roles is played by the immune system of the oral tissues, associated with general immunity, but also possessing significant autonomy and self-regulation.[42,43]

Indeed, the emerging inflammatory infiltrates in periodontal tissues are represented mainly by immunocompetent cells, which indicates the interest of the immune system in this process. The development of periodontitis is accompanied by an imbalance in the cytokine system. An increase in the content of proinflammatory cytokines is observed. The content of osteoclastogenesis cytokines also increases both in plasma and in gingival fluid. However, the sRANKL/OPG ratio increases unreliably.[44]

Once the inflammatory process is initiated, a characteristic infiltration of neutrophil cells occurs, followed by monocytic cells. Following the accumulation of inflammatory cells, various cytokines are produced during the inflammatory process, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), but IL-6 is one of the most well-known interleukins (figure 6).[45]

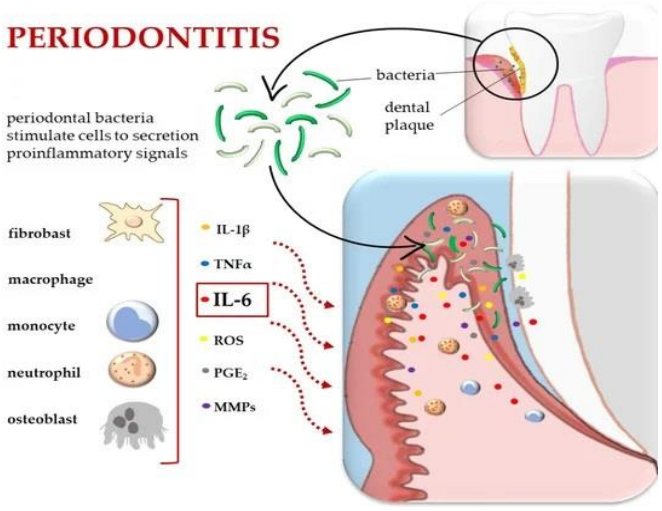

Figure 6. Inflammatory process in periodontitis. The influence of periodontal bacteria on cell activity and cytokine secretion. Abbreviations: IL-1β, Iterleukin 1 beta; TNFα, tumor necrosis factor-α; IL-6, Interleukin 6; ROS, reactive oxygen species; PGE_2, prostaglandin E2; MMP, matrix metalloproteinases. Illustration adapted some elements from previous work

Redistribution of immunocompetent cells, expressed by a decrease in the content of T-lymphocytes in venous blood and an increase in the number of T- and B-lymphocytes in the capillary blood of the periodontium. B-cell links of the immune system in the pathogenesis of periodontitis. Thus, the participation of the immune system in the pathogenesis of periodontitis development is undoubted, which makes the study of immune parameters and changes in their levels necessary in the examination and complex treatment of periodontitis.

In a healthy parodontal state, local provocation and weak host immune response are balanced. In this state, there are an appropriate number of infiltrating neutrophils in the gingival sulcus, as well as some resident immune cells in the gingival tissue, including Th17 cells and innate lymphoid cells.

However, if the immune pathogenicity of the local microbiota is increased by colonization of key pathogens, the host immune response is overactivated and tissue destruction is initiated. [46]

The interaction between the microbiota and all host cells leads to the first wave of cytokine secretion (1), which is mainly involved in amplifying the cascade of proinflammatory cytokines and recruiting, activating and differentiating specific immune cells. In addition, a group of cytokines (2), closely associated with the differentiation of a specific lymphocyte subset, is secreted by MNPs and APCs after stimulation by the microbiome. Each of these cell subsets secretes a distinct set of cytokines that can act as a positive feedback factor or a direct effector (3), ultimately leading to tissue destruction.[47,48]

Most published studies have focused on proinflammatory cytokines and pathogenic cell subpopulations, However, the functions of most classical pathogenic Th1 and Th2 cells and their associated cytokines in periodontitis have not been defined.[49]

With the advent of anti-cytokine biologics targeting the Th1 and Th17 pathways in autoimmunity, it is necessary to understand the potential implications for the treatment of periodontal disease in humans.[50]

Analysis of the existing periodontal literature and further research in light of these new findings may help to explain how the inflammatory response leads to periodontal damage. This knowledge is needed to develop immunomodulatory intervention strategies to maximize the protective and minimize the destructive aspects of the periodontal response pacienta

In summary, the periodontal-specific cytokine network and host immune response deserve further study. Research advances in this area may contribute to the development of tissue-specific therapeutic technologies and reduce the burden on patients with periodontal diseases, as well as the impact of local periodontal inflammation on associated systemic diseases.

Periodontal pathogenesis involves multiple interacting cytokines that govern cellular activity, immune responses, and tissue destruction associated with periodontitis. The strongest evidence for cytokine interactions in periodontal disease is for proinflammatory mediators such as IL-1β and TNF-α, and new information on cytokines relevant to other aspects of periodontal pathogenesis such as T cell regulation, bone cell activity, and leukocyte chemotaxis helps to understand how cytokine interactions affect lymphocyte function and how this contributes to periodontal pathogenesis.

Understanding the mechanisms of cytokine interactions and immune responses in the periodontium may help to understand the clinical course of the disease and develop new strategies for the treatment of periodontitis.

Key points

- It has been established that hyperimmune responses to periodontopathogenic microorganisms lead to the destruction of connective tissue and alveolar bone.
- It has been shown that in periodontitis, both innate and acquired immune mechanisms are involved in the pathological process.
- The stages of the inflammatory response and damage to periodontal tissues, which are determined by the balance of cytokines, are described.
- It is concluded that the development of periodontitis is accompanied by an imbalance in the cytokine system.

Conclusion. The etiology and pathogenesis of periodontal disease is quite complex, diverse and not yet fully disclosed. Cytokines are control and modulate the immune response in periodontitis.

Declarations

CONFLICT OF INTEREST

The author declare that they have no conflict of interest and there was no external source of funding for the present study.

ETHICAL APPROVAL

Not applicable.

Source of funding

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