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THE MAIN CYTOKINES OF INFLAMMATORY RESPONSE IN PERIODONTAL TISSUES, THERAPEUTICAL TARGETS: A REVIEW

Pavlenko Oleksiy,
Professor, Head of Department of Dentistry, National University of Health Care of P.L. Shupik, Doctor of Medical Sciences, Full professor
orcid.org/0000-0003-2097-4286
ResearcherID E-5025-2019, Scopus author ID 7006801448

Mochalov Iurii,
Associated professor, Department of Surgical Dentistry, Maxillofacial Surgery and Oncodentistry, Uzhhorod National University, Doctor of Medical Sciences, Docent
*orcid.org/*0000-0002-5654-1725
ResearcherID D-2957-2017
Scopus author ID 57208438870, E-mail: yuriy.mochalov@uzhnu.edu.ua

Sluchevska Olena,
PhD student of Department of Dentistry,
National University of Health Care of P.L. Shupik

Hasiuk Natalia,
Professor, Department of Therapeutical Dentistry, Ternopil National Medical University of I. Horbachevsky, Doctor of Medical Sciences, Full professor
orcid.org/0000-0002-6798-9090
ResearcherID Q-6326-2016, Scopus author ID 57192919609

Keian David,
Associated professor, Department of Surgical and Orthopeadical dentistry, Medical director of University Clinic, Kyiv International University, Candidate of Medical Sciences, Docent

Yurzhenko Anastasiya,
Associated professor, Department of Dentitry of Post-Diploma with course of Therapeutical and Orthopedical Dentistry, Uzhhorod National University, Candidate of Medical Sciences

Abstract. Nowadays, inflammatory and inflammatory-dystrophic periodontal diseases are widespread in Ukraine and in many other countries. Today we have no

complete and correct idea of the etiology and pathogenesis of periodontitis, thus, the ethiotropic therapy of inflammatory periodontal lesions does not solve the problem completely. Periodontitis and self-destruction of periodontal tissues also can trigger entire cascades of inflammatory and adaptive reactions in periodontal tissues. These reactions are regulated by cytokines and chemokines up to 44 names which interact with numerous receptors on cells, activate and cause the migration of macrophages, neutrophils and lymphocytes, as well as support the transformation and proliferation of the lymphocytes. Cytokines as therapeutic targets for the treatment of different diseases have been considered for a long time – that includes autoimmune diseases, collagenoses, tumors and cardiovascular lesions, in our opinion we should pay attention to such opportunities for the treatment of inflammatory and inflammatory-dystrophic periodontal lesions. The role of pro-iflammatory cytokines and chemokines in development of acute and chronic periodontitis was described for TNF-α, IFN-γ, TGF-β, IL-1 (IL-1α and 1β, interleukin 1 antagonist, IL-18), IL-2, IL-5 (eosinophilic colony-stimulating factor), IL-6, IL-8, IL-12, IL-17, IL-21, IL-23, IL-33. Anti-inflammatory properties were described for IL-4, IL-10, IL-13, IL-22, IL-35.

For different therapeutic needs a row of immunobiological experimental medicines was created, some of them were approved for clinical usage in cases of autoimmune and allergic diseases. They are: "Anakinra", "Mepolizumab", "Reslizumab", "Siltuximab", "Tocilizumab", "Sarilumab", "Clazakizumab", "Olokizumab", "Sirukumab", "Elsilimomab", "Levilimab", "HuMax-IL8", "Ustekinumab", "Secukinumab", "Ixekizumab", "Brodalumab", "Guselkumab", "Tildrakizumab", "Riskankizumab". Despite the lack of a complete picture of the pathogenesis of periodontal disease, some involved cytokines and their receptors in periodontal tissues are considered as markers of inflammation and regeneration processes, as well as therapeutic targets for the use of immunobiological blockers (monoclonal antibodies). Of course, such therapy is developed for systemic inflammatory and autoimmune diseases but the likelihood of their use in periodontology also looks promising.

Key words: periodontium, inflammation, pathogenesis, cytokines, regulation, treatment.

Introduction

Inflammatory and inflammatory-dystrophic periodontal diseases are widespread in Ukraine and in many other countries[35]. Centuries of research on this problem have allowed us to accumulate a significant amount of information about the etiology, mechanisms of development and therapeutic approaches to their treatment, but the problem is complex and multicomponent. Today we have no complete and correct idea of the etiology and pathogenesis of periodontitis[36]. Nowadays, the ethiotropic therapy of inflammatory periodontal lesions does not solve the problem completely[37]. This fact indicates the presence of more complex mechanisms of disease development and a number of "gaps" in the scientific information on this subject[38]. Therefore, the

[35] Mazur IP, 2017, p. 71.
[36] Klityns`ka OV et al., 2014, p. 217
[37] Popovich IY et al., 2017, p. 65
[38] Lang NP et al., 2018, p. 9

pathogenetic therapy of chronic inflammatory periodontal lesions remains one of the leading and effective areas of quality rehabilitation of periodontal patients[39].

It is established that factors of bacterial pathogenicity (such as hydrogen sulfitis, proteases, toxins, ammonia, etc.) which can affect the course of periodontitis and cause self-destruction of periodontal tissues, also can trigger entire cascades of inflammatory and adaptive reactions in periodontal tissues. These reactions are regulated by a group of local factors – cytokines and chemokines – up to 44 names which interact with numerous receptors on cells, activate and cause the migration of macrophages, neutrophils and lymphocytes, as well as support the transformation and proliferation of the lymphocytes[40 41].

Cytokines as therapeutic targets for the treatment of some diseases have been considered for a long time – they include autoimmune diseases, collagenoses, tumors and cardiovascular lesions, in our opinion we should pay attention to such opportunities for the treatment of inflammatory and inflammatory-dystrophic periodontal lesions[42].

The main cytokines in periodontal lesions development

Tumor necrosis factor-a (TNF-a). Another name is kachectin. This cytokine can exist in free form and in bound to membranes. It realizes its function by interacting with about 30 specialized receptors on cell surfaces. The predominant influence is in starting the processes of apoptosis but also in supporting the survival of individual cells, angiogenesis and differentiation of individual cells[43].

To date, its leading role is in the development and maintenance of inflammatory processes in various organs and tissues of the human body has been proven. This factor has a strong effect on bone remodeling (as shown in cases of rheumatoid arthritis), it regulates osteoclast precursor levels in the bone marrow by altering c-fms expression and activates osteoclasts by enhancing the signaling mechanism of NFAN-κB receptor activators[44]. TNF-α plays an important role in controlling the infectious process. Its releasing by macrophages is a crucial step in initiating the formation and maintenance of the existence of granulomas and plays an important role in protection against invasion, including intracellular parasites. TNF-α is also involved in the processes of leukocyte migration and filtration of immune complexes. The clear role of the factor in the tumor process is not known but its levels change at different stages of tumorigenesis. Its level increases with heart disease. It is believed that TNF-α contributes to the development of dyslipidemia and insulin resistance which are the leading mechanism for the development of atherosclerotic changes in blood vessels. TNF-α plays a leading role in the development of sepsis and peritonitis with its impact on the level of production of nitric oxide. Also, it plays a special role in the development of graft rejection reactions. Therefore, we can assume that tumor necrosis factor-α is a pleiotropic cytokine involved in numerous homeostatic and pathological mechanisms of the human organism[45].

TNF-α is preferably synthesized by macrophages; in small amounts it can be synthesized by T-lymphocytes, natural killers (NK), muscle cells, fibroblasts, vascular

[39] Danylevskyj NF et al., 2000, pp. 37, 111
[40] Yucel-Lindberg T et al., 2013, e7
[41] Lundmark A et al., 2019, p.216
[42] Surlin P et al., 2020, p.3
[43] Pan W et al., 2019, p.64
[44] Xiong G et al., 2019, p.6282635
[45] Kozak M et al., 2020, p.41

endothelium and osteoclasts. In the development of inflammatory lesions of the periodontium TNF-α plays a crucial role at the beginning of the inflammatory process when it is released from mastocytes and affected periodontal cells, triggers tissue destruction reactions, also it stimulates osteoclast proliferation leading to resorption of alveolar bone[46].

Interferons of group γ (IFN-γ) – belong to endogenous low molecular weight proteins with antiviral, immunomodulatory and antitumor properties. By their structure, they are glycoproteins that are produced mainly by T-lymphocytes. According to its function, this class of interferons is antitumor, immunomodulatory, radioprotective, cytostatic. The mechanism of action of IFN-γ is related to the effect on enzymes that control the synthesis and destruction of nucleic acids – synthetases and nucleases; they affect the synthesis of a special cellular protein that inhibits the translation and replication of viruses. The immunoregulatory effect of IFN-γ is manifested in increased phagocytic activity of macrophages, enhanced spontaneous activity of T-killers and cooperative immune response against virus-induced tumor cells. Immune interferon (γ-interferon, T-interferon), produced mainly by T-lymphocytes, is a cytokine. It is characterized by antiproliferative activity, as well as increases the activity of macrophages and cytotoxicity of NK cells[47]. IFN-γ is synthesized by stimulated lymphocytes upon re-encounter with a homologous antigen under the influence of mitogens, which may act as viruses, some species of bacteria, actinomycetes, rickettsiae, chlamydia, mycoplasmas, protozoa, nucleic acids, polysaccharides and lypopolysaccharides[48].

The role of IFN-γ in the development of inflammatory periodontal lesions is not fully understood, a number of studies indicate completely opposite data. There was shown a direct relationship between the intensity of the inflammatory response in the periodontium and the level of IFN-γ in the gingival fluid, other studies indicate a possible relationship with the existing comorbid status in patients and indicate an increase in this type of interferon with periodontal healing. It is clearly established that the level of IFN-γ changes in cases of disorders of the periodontal tissues but its role and indicator properties in periodontal disease are unclear now[49].

Transforming growth factor-β (TGF-β) is a cytokine of systemic action which is involved in numerous physiological, pathological and adaptive reactions in the human body. It exists in three forms β1, β2 and β3. The β1 fraction belongs to the so-called superfamily of transforming growth factor (more than 40 proteins), including inigbins, activins, anti-Mullerian hormones, bone morphogenetic proteins, growth differentiation factors, glial neurotrophic factors and other regulatory proteins. TGF-β exerts its influence through the regulation of apoptosis processes, regulates the cell cycle, influences the course of immunological reactions through T-cells and blocks the activation of macrophages and lymphocytes. The β1 form is a major factor in stimulating soft tissue regeneration and wound healing. TGF-β is involved in the regulation of the tumor process, systemic connective tissue lesions, cardiovascular system and the development of degenerative diseases of the nervous system[50]. Transforming growth factor-β is synthesized by many

[46] Yamazaki M et al., 2018, p.352
[47] Labzin LI et al., 2016, p. 37
[48] Nanda RPG et al., 2019, p.56
[49] Maulani C et al., 2019, p. e5106
50 Gomes FI et al., 2016, p.2

cells, which may also have receptors for such a protein. A significant amount of this factor is synthesized by macrophages.

In the development of inflammatory lesions of the periodontium role of TGF-β is assigned in the initial stages as a signaling between inflammatory cells, and as an initiator of healing and adaptive reactions. TGF-β1 decreases with intense inflammation of periodontal tissues, and increases during the healing phase (recovery of soft tissues and bone tissue). An increase in TGF-β2 levels in the gingival fluid is observed when the regeneration of periodontal tissues slows down[51].

Interleukin-1 (IL-1) system. This group of interleukins includes 11 related cytokines (IL-1α and 1β, interleukin 1 antagonist, IL-18, IL-36α, IL-36β, IL-36γ, IL-36RA, IL-37, IL-38, IL-33) – they are powerful pro-inflammatory cytokines that are synthesized by different cells. Exceptions are IL-37 and IL-38 which have anti-inflammatory properties. IL-1 can affect all organs and systems of the body (both independently and in interaction with other pro-inflammatory factors) – they are the main pathogenetic mediators of autoimmune, inflammatory, infectious and degenerative processes. This group of cytokines mainly stimulates T-lymphocytes and maturation of B-lymphocytes, causes pro-inflammatory and pyrogenic action, enhances the function of neutrophilic granulocytes, provides the links between the immune, nervous and endocrine systems[52]. IL-1β, IL-18 is synthesized by monocytes, macrophages, dendritic cells, and IL-1α is synthesized by endothelial cells, keratinocytes, fibroblasts, platelets, epitheliocytes and astrocytes.

In the development of inflammatory lesions of the periodontium this group of cytokines is actively involved. In this case, IL-1α acts as a signaling molecule for tissue damage to the immune system, enhances the course of inflammatory reactions, and stimulates the release of other pro-inflammatory cytokines by other cells. In general, it is a marker of the intensity of the inflammatory process in the periodontium, which can enhance the resorption of bone tissue by signaling the presence of bacterial antigens in the inflammatory focus. IL-1β also acts indirectly by stimulating the production of pro-inflammatory mediators IL-6 and prostaglandin E2, and increases the activity of neutrophilic granulocytes. This fraction of the cytokine IL-1 plays a key role in the course of inflammatory reactions, enhances the resorption of bone tissue of the jaws. The growth of IL-18 is also found in the gingival fluid during inflammatory processes in the periodontium and there is a direct correlation of its level with clinical signs[53] [54]. As a therapeutic target, IL-1 was used in the development of the medicine "Anakinra" (a blocker of receptors for IL-1) which was created for the treatment of rheumatoid arthritis. Also known studies on the development of antibodies to IL-18[55].

Interleukin-2 (IL-2) is a mediator of inflammation and immunity. It is basic in the IL-2 family (also includes IL-4, IL-7, IL-9, IL-15 and IL-21) - the main function is to activate the differentiation of T-helpers and T-killers, NK and immunoglobulin synthesis B-lymphocytes. This interleukin is highly important in maintaining the function of antitumor and transplant immunity, as well as the containment of certain parts of the

[51] Um S et al., 2018, p.8
[52] Talvan ET et al., 2017, p. 09
[53] De Alencar JB et al., 2020, p.e0227905
[54] Rodríguez-Montaño R et al., 2015, p.39
[55] Zhang Y et al., 2021, p.15.

immune system. It is produced by T-lymphocytes, transformed T- and B-lymphocytes, leukemic cells.

In the development of inflammatory lesions of the periodontium IL-2 was not described separately, its growth was determined during the transformation of T-lymphocytes into Th1 under the influence of pathogens from the periodontal pocket, while along with the synthesis of IL-2. As a therapeutic target for the treatment of periodontal disease at the moment the development of science IL-2 is not promising[56].

Interleukin-4 (IL-4) – a cytokine that stimulates T-helpers, enhances the proliferation of B-lymphocytes and their conversion into plasmocytes, increases the production of immunoglobulin E (IgE), and reduces the production of individual T-lymphocytes, macrophages, dendritic cells and IFN-γ production. Therefore, it acts as an anti-inflammatory cytokine. Interleukin-4 is involved in the development of allergic reactions, promotes intensive tumor growth, its participation in the development of neurodegenerative diseases, as well as in the development of the infectious process in HIV. IL-4 is produced by mast cells, T-helpers, eosinophils and basophils.

In the development of inflammatory lesions of periodontal tissues IL-4 participates as an inhibitor of the inflammatory process, so in the active duration of periodontitis its level in the gingival fluid decreases sharply. In periodontal tissues IL-4 inhibits the proliferation of Th2 cells which reduces inflammatory process and indirectly promotes tissue repair[57].

Interleukin-5 (IL-5, eosinophilic colony-stimulating factor) is a pro-inflammatory cytokine that causes the maturation and activation of eosinophils, as well as activates B-lymphocytes. It is described that activated eosinophils are able to damage surrounding cells (including the vascular wall) by direct cytotoxic effects and the involvement of other cells. Eosinofils can secrete highly toxic cytoplasmic proteins – basic alkaline protein, eosinophilic cationic protein, eosinophilic peroxidase, eosinophilic neurotoxin, and additionally secrete a number of cytokines.

In the development of inflammatory lesions of the periodontium IL-5 has not been studied separately. Its level increases along with other pro-inflammatory and anti-inflammatory cytokines (IL-1, IL-4, IL-6, IL-10 and IL-13) upon activation of Th2 cells in response to the development of the inflammatory process. IL-5 is therapeutical target in control of inflammation. Monoclonal antibodies to IL-5 – "Mepolizumab" and "Reslizumab" were developed and introduced into clinical practice in some countries[58].

Interleukin-6 (IL-6) – is one of the most powerful pro-inflammatory mediators in acute inflammation. In muscle tissue, it can act as an anti-inflammatory cytokine (myokin). IL-6 affects almost all organs and systems – blood, liver, immune and endocrine systems, metabolism. It causes the mobilization of energy reserves which is necessary when the body temperature rises, affects muscle and adipose tissue, stimulates the proliferation and differentiation of B- and T-lymphocytes, increases the synthesis of C-reactive protein. Excessive production of IL-6 is observed in cases of massive injuries, burns and autoimmune processes. IL-6 triggers joint damage, activates osteoclasts, which causes bone damage.IL-6 is secreted by macrophages, epitheliocytes, keratinocytes after activation by pathogen-bound molecules – particles of viruses, bacteria, fungi and some lypo-polysaccharides.

[56] Costantini E et al., 2020, p.69
[57] Tsai CC et al., 2007, p.7
[58] Ramadan DE et al., 2020, p.483

In the development of inflammatory lesions of the periodontium IL-6 takes an active part, as evidenced by the increase in its level in the gingival fluid in the active course of inflammation and fall in the attenuation of the inflammatory process. IL-6 enhances the intensity of inflammation when activating Th2 and Th17 cells. Separately, IL-6 interacts with bone tissue through the RANK system, which stimulates osteoclast proliferation and supports bone resorption[59]. IL-6 is a therapeutic target for the development of specific antibodies, as well as blockers of its receptors – "Siltuximab", "Tocilizumab", "Sarilumab", which are approved for use in the clinic, studies are continued for medicines "Clazakizumab", "Olokizumab", "Sirukumab", "Elsilimomab","Levilimab" and others. Also, the effect of inhibition of IL-6 production in neurons was obtained with the use of the flavonoid luteolin[60].

Interleukin-8 (IL-8) is also a pro-inflammatory cytokine (chemokine). It is a powerful endogenous chemoattractant (causes migration of leukocyte cells – neutronphilic granulocytes, macrophages, lymphocytes and eosinophils), acts as an activator of leukocytes, enhances the generation of reactive oxygen species. It also plays an important role in the mechanisms of innate immunity. IL-8 is involved in the processes of mitogenesis, inhibition of angiogenesis, inflammation, chemotaxis, neutrophil degranulation, leukocyte activation, tissue regeneration and remodeling, and calcium homeostasis. IL-8 is synthesized by macrophages, endothelial cells, fibroblasts and epithelial cells.

In the development of inflammatory lesions of the periodontium IL-8 participates at the early stages of the inflammatory process by stimulating the chemotaxis of inflammatory cells to the affected tissues of the marginal periodontium. Therefore, with inflammation in the periodontal tissues the level of IL-8 in the gingival fluid increases[61]. As a blocker of IL-8, monoclonal antibodies "HuMax-IL8" were developed, which continue to be studied.

Interleukin-10 (IL-10) - is the main anti-inflammatory cytokine which is a key regulator of the inflammatory response and acts as an antagonist for a significant list of pro-inflammatory factors and mediators. IL-10 has a pleiotropic anti-inflammatory effect which is to inhibit IFN synthesis by inhibiting T-lymphocyte proliferation, slows the synthesis of TNF-α and IL-6 but is able to stimulate IgE thereby enhancing humoral immunity. IL-10 is also an important regulator of tolerance to transplanted organs, protection of tissues from damage during ischemia and inhibition of neurodegenerative diseases. IL-10 is synthesized in monocytes, lymphocytes and mast cells[62].

In the development of inflammatory of the periodontium IL-10 takes an active part as an inhibitor of inflammatory reactions, by inhibiting the production of other pro-inflammatory cytokines. Its concentration in the gingival fluid is inversely proportional to the intensity of the inflammatory reaction. IL-10 in the process of inflammation in the periodontium is secreted by activated Th2 cells, T-reagins; IL-10 affects macrophages, polymorphonuclear leukocytes and periodontal fibroblasts, which inhibit the secretion of TNF-α, IL-6, prostaglandins E2, IL-1β, thereby blocking the processes of activation and reproduction of osteoclasts and, accordingly, the resorption of alveolar bone tissue

[59] Batool H et al., 2018, p.8531961
[60] Chatzopoulos GS et al., 2017, p.457
[61] Finoti LS et al., 2017, p. e6932
[62] Chatzopoulos G et al., 2018, p.e11

[63]. Since the 90s of the XX century, IL-10 is considered as a therapeutic target of various inflammatory processes, studies of the use of recombinant human IL-10 are in progress.

Interleukin-12 (IL-12) belongs to the family of heterodimeric cytokines (it also includes IL-23, IL-27, IL-35). IL-12 is a promoter of the inflammatory process, a key cytokine of the cell-mediated immune response, stimulates the proliferation of activated T-lymphocytes, NK cells and cytotoxic cells, production of IFN-γ and TNF-α, inhibits the synthesis of immunoglobulin. IL-12 also inhibits angiogenesis and deepens autoimmune responses. IL-12 is secreted by activated B-lymphocytes, monocytes and macrophages, neutrophils and dendritic cells[64].

With the development of inflammatory lesions of the periodontium in the gingival fluid can be determined by an increase in the concentration of IL-12. It is involved in the differentiation of Th0 cells into Th1, which become producers of IFN-γ, IL-2 and TNF-α. IL-12 is a therapeutic target for monoclonal antibodies – "Ustekinumab"[65].

Interleukin-13 (IL-13) – is similar to IL-4 in structure and function, and plays an important role in the development of a number of allergic diseases (including respiratory lesions), the main mechanism of action – stimulation of IgE synthesis through activation of B-lymphocytes, also under the influence of IL-13 increases the secretion of mucus components by mucous membranes which increases bronchial lavage. Also, IL-13 is a leading mediator in the formation of inflammatory granulomas in tissues during helminth invasion, and others. In addition, IL-13 is a stimulator of migration and survival of epithelial cells, production of nitric oxide by airway epithelium, activation of macrophages, transformation of fibroblasts into myofibroblasts which leads to the accumulation of collagen and the development of fibrotic changes in the respiratory system. IL-13 is secreted from T-helpers, CD4-cells, NK, mast cells, basophils, eosinophils and nuocytes.

In the development of inflammatory and lesions of the periodontium IL-12 has not been studied separately, it acts as a synergist of IL-4 and its synthesis is enhanced by stimulation of IL-4 Th2 cells. IL-13 is a therapeutic target in the treatment of bronchial asthma, the monoclonal antibody medicines "Tralokinumab" and "Lebrikizumab" have been developed[66].

Interleukin-17 (IL-17) – has a family of related cytokines (cytokines of the so-called "cysteine node", including IL-17B, IL-17C, IL-17D, IL-17F and IL-17E, also known as IL-25). IL-17 is a pro-inflammatory mediator that is also involved in the development of allergic reactions. The IL-17 family is involved in the regulation of numerous protective immune responses by stimulating the production of many signaling molecules – IL-6, colony-stimulating factor-3 (granulocytes), colony-stimulating factor-2, IL-1β, TNF-α, chemokines (IL-8, GRO-α, MCP-1 – monocyte chemotaxis factor) and prostaglandin E2, – from many cells. Cytokines-17 are involved in the development of psoriasis and bronchial asthma, regeneration of nervous tissue after ischemic lesions[67]. IL-17 is secreted from many cells – neural tissue, muscular tissue, T-lymphocytes, peripheral blood vessels. During inflammation in the periodontium its source is activated Th17 lymphocytes.

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[63] Shi T et al., 2020, p.357
[64] Tsai IS et al., 2005, p.40
[65] Issaranggun Na Ayuthaya B et al., 2018, p.75
[66] Beklen A, 2017, p.380
[67] Isaza-Guzmán DM et al., 2015, p.99

In the development of inflammatory lesions of the periodontium IL-17 is involved at different stages, as evidenced by its growth in the gingival fluid during inflammation; its main effect is to maintain the overall inflammatory response and support the proliferation of osteoclasts and subsequent resorption of bone tissue of the dental alveoles[68]. Therapy aimed at blocking IL-17 is a real direction in medicine, the medicines with monoclonal antibodies "Secukinumab", "Ixekizumab" and "Brodalumab" were developed and tested for the treatment of systemic lesions.

Interleukin-21 (IL-21) is a homologue of IL-2, IL-4 and IL-15. IL-21 regulates the processes of antitumor and antiviral protection, also reduces the intensity of allergic reactions. IL-21 stimulates the growth and differentiation of T cells, B cells (including the formation of memory B-cells), increases the activity of NK. IL-21 is considered a potential direction for the treatment of HIV infection. IL-21 is produced by activated T lymphocytes and can also be produced by tumor cells in cases of Hodgkin's lymphoma.

With the development of inflammatory lesions of the periodontium in the gingival fluid can be found elevated levels of IL-21 which correlates with the intensity of inflammation. Available data on its effect on the level of tissue destruction in periodontitis, IL-21 is also considered as a biomarker of inflammation in periodontitis[69]. IL-21 and its receptors are considered as a therapeutic target for the development of immunobiological medicines for the treatment of autoimmune and systemic inflammatory diseases.

Interleukin-22 (IL-22) is a homologue of IL-10. It is synthesized by many cells in the site of inflammation, mainly affects non-hematopoietic cells – stroma and epithelium, supports cell survival, proliferation and synthesis of antimicrobial substances, as well as tissue regeneration processes. Dysfunction of IL-22 is observed in the development of autoimmune diseases – rheumatoid arthritis, systemic lupus erythematosus, psoriasis. IL-22 simultaneously has pro-inflammatory properties and performs the function of protecting cells from the effects of the inflammatory process. IL-22 is produced by T cells (Th17 series), NK, neutrophils, macrophages and dendritic cells. IL-22 plays a key role in the synthesis of human β-defensin-2 (hBD-2).

In the development of inflammatory and inflammatory-dystrophic lesions of the periodontium IL-22 acts as a synergist of anti-inflammatory IL-10, data are available on its positive effect on the regeneration of periodontal tissues. In cases of chronic periodontitis, the level of this cytokine increases in the gingival fluid[70].

Interleukin-23 (IL-23) is a pro-inflammatory cytokine belonging to the IL-12 family. IL-23 stimulates T cells to proliferate and expand, as well as indirectly, due to increased levels of IL-17, IL-21, IL-22 and colony-stimulating factor-2, affects protection against extracellular parasites – bacteria and fungi, the formation of barrier immunity and recognition of antigens, the development of autoimmune processes in nervous tissue and its regeneration after hemorrhage. Stimulates the growth and formation of blood vessels. IL-23 plays role in the development of psoriasis, allowed participation in the development of atherosclerosis and cardiovascular lesions. IL-23 is secreted by activated T cells, monocytes, macrophages and dendritic cells.

In the development of inflammatory lesions of the periodontium IL-23 participates as a pro-inflammatory cytokine, the level of which increases in patients with chronic

[68] Wankhede AN et al., 2019, p.8
[69] Lokhande RV et al., 2019, p.24
[70] Sidharthan S et al., 2020, p.503

and acute periodontitis[71]. IL-23 is a therapeutic target for a number of autoimmune diseases, are monoclonal antibodies "Ustekinumab", "Guselkumab", "Tildrakizumab" and "Riskankizumab" have been developed.

Interleukin-33 (IL-33) – belongs to the IL-1 family. It is a pro-inflammatory cytokine that has pleiotropic protective responses. In the extracellular environment, it stimulates the secretion of cytokines of the IL-2 family from T-helpers, mast cells, eosinophils and basophils. IL-33 affects the function of keratinocytes in the skin, especially in the development of allergic reactions, causes itching. In the middle of the cell, it acts as a nuclear factor that promotes the formation of the DNA helix, which is found in the endothelium of small vessels with prolonged inflammation. The role of IL-33 has been proven in the development of bronchial asthma, allergies, endometriosis, allergic rhinitis (hay fever), chronic colon inflammation, energy mobilization from adipose tissue. IL-33 is secreted by numerous cells, including fibroblasts, mast cells, dendritic cells, macrophages, osteoblasts, endothelial cells, and epithelial cells.

In the development of inflammatory lesions of the periodontium IL-33 plays a role in increasing inflammation, indirect stimulation of bone resorption, as well as the possibility of increasing the secretion of IL-33 in the presence of periodontal pathogen Porphyromonas gingivalis[72]. IL-33 is considered as a therapeutic target for the treatment of periodontitis in elderly patients, so today the development of monoclonal antibodies to interleukin itself, as well as to its ST2 receptors is in progress.

Interleukin-35 (IL-35) is a newly discovered anti-inflammatory cytokine that belongs to the IL-12 family. Its influence on the inflammatory process is an indirect effect on the reproduction and differentiation of lymphocytes, interaction with T-helpers. Genetic defects that affecting the expression of this cytokine lead to the development of a number of severe autoimmune diseases (systemic lupus erytemotosus, psoriasis, colitis, type I diabetes, multiple sclerosis, autoimmune hepatitis). Experimentally established that increased expression of IL-35 leads to the activation of chronic viral infections. An increase in its level was also observed in the development of some malignant tumors. IL-35 is normally produced by T- and B-lymphocytes, but upon activation it can be expressed in vascular endothelium, smooth myocytes, and others.

In the development of inflammatory and inflammatory-dystrophic lesions of the periodontium IL-35 plays the role of inhibitor of inflammatory processes and stimulator of periodontal tissue repair and normalization of their function[73]. IL-35 itself is considered as a therapeutic target, for which the creation of recombinant drugs is hypothetically possible.

Conclusions

Thus, at the current moment of development of medicine, according to the results of the study of the role of individual cytokines in the development of inflammatory and restorative reactions in periodontal tissues, information on pro-inflammatory and anti-inflammatory function has been established. Despite the lack of a complete picture of the pathogenesis of periodontal disease, some involved cytokines and their receptors in periodontal tissues are considered as markers of inflammation and regeneration processes, as well as therapeutic targets for the use of immunobiological blockers

[71] Sadeghi R et al., 2018, p.80
[72] Rodrigues WF et al., 2017, p.4
[73] Schmidlin PR et al, 2021, p. 139

(monoclonal antibodies). Of course, such therapy is developed for systemic inflammatory and autoimmune diseases but the likelihood of their use in periodontology also looks promising.

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