World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-19, February 2023
ISSN: 2749-3644

THE ROLE OF INFLAMMATION FACTORS IN THE MECHANISMS OF PROTECTION AND DESTRUCTION OF PERIODONTAL TISSUES

Kim Vitaly Eduardovich
Ass. Department of hospital orthopedic dentistry place of work Tashkent State Dental Institute
Khabilov Nigman Lukmonovich
Prof. Head Department of hospital orthopedic dentistry. Tashkent State Dental Institute
Boboev Kodirjon Tukhtaboevich
Doctor of Medical Sciences Prof. RSNPMCG
Gulmukhamedov Pulat Bakhtierovich
Doctoral Student of The Basic Doctoral Program Dsd Samara State Medical University

Article history:

Received: December 8th 2022
Accepted: January 8th 2023
Published: February 4th 2023

Abstract:

The occurrence and course of any disease of an infectious nature is determined by the strength of the body's response [18, 16]. The nature of this response depends on the antigenic specificity of previously acquired immunity and is largely determined by the human genotype [10, 16]. At the same time, only a part of the observed reactions of the body to infection can be considered as protective [15].

Keywords:

The occurrence and course of any disease of an infectious nature is determined by the strength of the body's response [18, 16]. The nature of this response depends on the antigenic specificity of previously acquired immunity and is largely determined by the human genotype [10, 16]. At the same time, only a part of the observed reactions of the body to infection can be considered as protective [15].

In addition, reactions of a neutral nature often occur: useless from the point of view of protecting the body, but depleting the resources of the immune system [13], as well as autotoxic reactions that cause massive damage and death of one's own cells and tissues [11, 14]. Often, it is autotoxic reactions that determine the pathophysiological picture of the disease as a whole.

Studies in the field of etiology of both aggressive and chronic periodontitis have led to the discovery of the fact of a sharp increase in the activity of matrixins (matrix proteinases synthesized, in particular, by fibroblasts and macrophages) in the event of inflammation of periodontal tissues of any nature [7, 29, 36, 22, 26 , 13, 12].

Especially significantly - hundreds and thousands of times, this increases the activity of neutrophil collagenase MMP8 and gelatinase MMP9: enzymes involved in the final stages of collagen degradation [15, 14, 25]. On this basis, most researchers make a conclusion about the autoproteolytic nature of the degradation of the periodontal connective tissue matrix underlying periodontitis [15, 16].

Important details of the molecular mechanism of the degradation of the periodontal ligament remain unclear, but it seems that lymphocytes act as an inducer of MMP hyperproduction and hyperactivation, which, in response to the invasion of pathogenic bacteria, migrate to the areas of the affected periodontium and release pro-inflammatory lymphokines. Some of these lymphokines act as inducers on resident fibroblasts and macrophages. The functional affiliation of lymphocytes and the antigens to which they are specific remain unknown, however, it can be assumed that the cause of the degradation of the periodontal ligament is the excessive activity of lymphocytes infiltrated into the infection focus, aimed at eliminating invasion [15, 7].

At the same time, the role of bacterial proteinases as destroyers of collagen and other matrix components is considered as a signal, although sometimes it is also assigned significant importance [15]. This point of view is largely contradicted by the fact that the increase in the activity of collagenases that are directly capable of attacking native collagen, for example, MMP1 and MMP13, has not been associated with periodontal disease in any study [16,16]. Activation of terminal matricins alone, even

reaching several orders of magnitude compared to the baseline, is not able to affect the integrity of the collagen base of the periodontal ligament [172].

When considering the effect of MMP8 and MMP9 on the degradation of the periodontal connective tissue matrix, an important issue is the regulatory mechanism for increasing their activity [17,18]. research,

real-time PCR and ELISA showed a significant increase in the level of MMP8 and MMP9 mRNA [13], as well as corresponding protein products [20, 26].

However, these indicators only indirectly reflect the level of activity of the corresponding enzymes [27]. The fact is that most of the matricins of any normal tissue are in the form of precursors devoid of enzymatic

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-19, February 2023
ISSN: 2749-3644

activity [28]. Activation of precursors occurs via a cascade mechanism, and the activation of terminal MMPs (gelatinases and stromelysins) is achieved mainly due to the proteolytic activity of matrixins located at the beginning of the signaling pathway [21].

Thus, overproduction of MMP8 and MMP9 precursors, which undoubtedly takes place during periodontal inflammation, is not a sufficient condition for an increase in the activity of these proteases: this also requires preliminary activation of MMP1, MMP2, and MMP3 [17, 20]. Moreover, the presence in the tissues of MMP inhibitors - TIMP1, TIMP2, TIMP3 and TIMP4, the total concentration of which is several times higher than the concentration of any MMP, makes it possible to completely suppress the activity of even those MMP molecules that have undergone proteolytic activation and do not contain a propeptide (usually , the propeptide exhibits a high inhibitory activity against its own MMP) [21, 22].

But published experimental data do not provide any evidence that such processes take place in periodontal inflammation [239, 240]. However, it must be borne in mind that

The RT-PCR, ELISA, and FA methods used in modern works practically do not allow one to distinguish the active form of MMP from its precursor [20]. This task is all the more difficult for primary MMPs (MMP1, MMP2, and MMP3), whose concentration in tissues is significantly lower than for terminal MMPs (MMP8 and MMP9) [28].

Summarizing the above, it should be noted that the role of MMP8 and MMP9 in the degradation of the periodontal ligament and alveolar bone needs to be specified, although the statistical relationship between the overproduction of these matrixin precursors and the severity of periodontitis can be considered proven [16].

Another point well covered in the literature regarding the role of MMP8 and MMP9 in the development of periodontitis is the mechanism of activation of their synthesis by lymphokines [26]. There is irrefutable evidence that the production of MMP8 and MMP9 in the affected areas of the periodontium correlates with an increase in the concentration of lymphokines of an acute nonspecific response to invasion (Thl-type): ILip, IL12, IL18, TNFa, osteoclast surface receptor ligand (RANKL) and osteoprotegerin (OPG) there.) [16].

On the contrary, an increase in the concentration of lymphokines stimulating an antigen-dependent response (Th2-type): IL10 and IL4 correlates with a decrease in the production of MMP8 and MMP9 [19]. At the same moment, there is an increase in the production of IL17, a factor that stimulates the healing of the wound surface after the infection has been eliminated [10]. When studying the local level of these mediators in periodontal tissues, this process can be observed mainly at the stage of periodontitis remission [12].

There is also direct evidence that stimulation of fibroblasts cultured in vitro with TM-lymphokines: IL1p, IL12, IL18, TNFa and RANKL increases the level of accumulation of precursors of metalloproteinases by 2-3 orders of magnitude, first of all, MMP8 and MMP9 (the results of the determination of mRNA and the precursor proteins encoded by them coincide) [18, 19]. Thus, lymphokines

should be considered as one of the key factors for activating the production of MMP precursors in response to invasion [11].

The described model is consistent, but not all of its points are experimentally confirmed. In addition, the functions of various cell types of the host organism require specification [11]. First of all, the distribution of the roles of fibroblasts and regional macrophages in the production of primary mediators of the Th1 response, as well as MMP, remains unclear [11].

At the same time, it should be taken into account that although macrophages, like periodontal fibroblasts, are residents of the periodontal tissue and cannot enter the circulation, the mechanism for replenishing their pool in the tissue is different, as a result, the ratio of the number of these cell types can vary widely [120, 132]. First, the Ty1 response itself stimulates the influx of

monocytes from the circulation, which can increase the ratio of the number of macrophages and fibroblasts by an order of magnitude or more compared to the norm [14].

The key role in this process of demobilization of monocytes from the bloodstream is due to the fact that the number of fibroblasts in the periodontal tissue cannot be significantly changed due to physiological functions [18]. It should be taken into account that osteoclasts responsible for alveolar bone resorption are derivatives of monocytes belonging to macrophage cells [19].

Second, neutrophils, the most numerous population of blood cells, are an essential element of the antibacterial response involving factors recruited from the central circulation [6, 33]. The function of neutrophils is to deliver oxidants to the site of infection - reactive oxygen species with high bactericidal activity [5]. In this case, the neutrophils themselves die.

IL8 is the main chemotactic factor in attracting neutrophils to the site of infection [55]. There are numerous experimental data on a local rise in the level of IL8 in inflammatory foci, including in chronic periodontitis [37], which makes some authors classify it as a factor in the Th1 response.

According to other authors, this point of view is not entirely accurate, since the accumulation of IL8 in infected tissues usually occurs over a long period (several days), which is not comparable with the

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-19, February 2023
ISSN: 2749-3644

duration of the protective phase of the Thl response [63]. Rather, the IL8-dependent neutrophilic response can be characterized as a reaction designed to cover the pause between the protective phases of the Th1 (antigen-independent) and Th2 (antigen-dependent) responses [66]. In the case of periodontitis of any form, hyperproduction of IL8 can be considered as a marker indicating the failure of the immune system's attempts to contain the infection due to the Thl response [7].

At the same time, the cell type that is the main source of IL8 remains unknown [3]. It is also undoubted that prolonged and massive infiltration of excess neutrophils into the periodontal tissue cannot provide a protective effect of the immune response [68], although it is possible that at the first contact of neutrophils with bacteria, they are able to restrain the development of infection for a certain period and even completely eliminate the foci of invasion. [1].

Most of the experimental studies of the mechanisms of IL8 synthesis induction in periodontitis were performed on a human gingival epithelial cell model, in particular, on the immortalized OBA-9 cell line or on primary gingival fibroblasts.

An example of such work is the article by Savitri IJ et al. (2014). The authors set out to investigate the effect of irzogladin maleate (IM), which is a well-known regulator of inflammation, on the interaction of gingival epithelial cells with the periodontopathogen P. gingivalis. It has been shown that IM removes the effect of induction of IL8 synthesis by P. gingivalis or its purified polysaccharide on OBA-9 cell culture ($P < 0.01$) [208].

In the work of Hajishengallis G. et al. (2015) describes a study of lymphokine production in an animal model of periodontitis. Using several different models, the authors concluded that IL1, TNFa, prostaglandins, complement components, and RANKL are the most important factors in assessing periodontal health. At the same time, the authors observed differences in the effectiveness of the induction of the synthesis of these factors by various bacterial pathogens, and they tend to consider dysbacteriosis to be the most common cause of periodontitis. As systemic factors of the human body that affect the tendency to periodontitis, the authors name diabetes and differences in the adhesiveness of leukocytes [33].

In the work of Korean authors Bae WJ et al. (2015) studied the effect of the hypoxia factor HIF2a on the inflammatory response and differentiation of osteoclasts, in particular, the correlation between the concentration of HIF2a and the local level of inflammatory cytokines and proteolytic enzymes during stimulation of human gingival fibroblast culture with bacterial lipopolysaccharide (LPS) and nicotine. It was found that cells from patients with CGP release more HIF2a in response to stimulation with nicotine and LPS, and the response increases with time and increases with increasing stimulus concentration [32].

Brazilian authors Correa JD et al. (2014) describes a study of the influence of brain-derived neurotrophic factor (BDNF) on the course of periodontitis, which has highly sensitive targets outside the nervous system, in particular, in the periodontal ligament, dental pulp and odontoblasts [84]. However, physiological experiments to study the effect of BDNF on the condition of the periodontium at the beginning of the study were limited to a model of mechanically damaged periodontal regeneration. Its role in the development of periodontitis was investigated for the first time. The study involved a sample of patients with CGP (28 people) and with a healthy periodontium (29 people). The ELISA method revealed an excess of BDNF levels in periodontal washings in the CGP group compared to the control. In both samples, the content of BDNF was in feedback with the local level of IL10. The data obtained indicate the possible involvement of BDNF in the development of periodontitis (or the degree of protection from it), however, the specific role of this factor remains unclear.

In the work of the Swedish authors Khalaf H. et al. (2014) states that cytokines and chemokines are differently expressed in patients with periodontitis and show the possible role of TGF01 as a disease marker. With this in mind, they conducted a comprehensive study of the representation of various cytokines and lymphokines in the blood serum, saliva and periodontal lavage of patients with periodontitis and a control sample of individuals with healthy periodontium. The most significant difference in the sample of patients was a reduced level of IL6 in the blood and saliva. On the contrary, the level of IL8 in the blood did not differ, in saliva it was reduced, and in periodontal washings it was increased. Lymphokine of T-cell origin IL2 in the blood and saliva of patients of both samples was contained in the same concentration, but its content in periodontal washings of patients was significantly reduced. An unexpected result was a significant increase in the level of TGF01 in the blood, saliva and periodontal washings of patients with CGP. The authors consider TGF01 to be one of the main candidates for the role of a factor mediating the systemic effects of periodontal inflammation [160].

Laboratory studies confidently confirm the correlation between the presence of an active inflammatory process in periodontal tissues and an increase in the concentration of Thl-type lymphokines and MMP in the affected areas [2]. We can equally confidently say that the successful overcoming of the crisis in the development of bacterial infection of the periodontium is accompanied by an increase in the level of Th2-type lymphokines.

However, the identification of these correlations does

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-19, February 2023
ISSN: 2749-3644

not make it possible to predict the course of the disease, but only allows alternative methods to confirm the diagnosis that periodontists successfully make based on the analysis of the clinical signs of the disease: the depth of periodontal pockets, the presence of bleeding and suppuration, and pathological tooth mobility [34].
Moreover, many authors allow a simplified approach to the interpretation of data from the analysis of the profile of lymphokines and MMP on the periodontium, not trying to look for causal relationships between the detected reactions, but limiting themselves to the detection of a statistical correlation. As a result, there are statements that the Thl response (production of IL10, TNFa, IL12, IL18, RANKL, as well as the subsequent synthesis of MMP8 and MMP9) is the cause of periodontitis, and its suppression by any means should contribute to recovery [16].
On the contrary, the Th2 response, according to these authors, is the reason for the successful overcoming of the disease [32, 27]. Meanwhile, it is obvious that in itself the identification of statistically significant correlations between certain parameters does not say anything about causal relationships between them. In addition to logical constructions, a necessary element for identifying such regularities is the analysis of the time sequence of the onset of reactions [31].
In view of the foregoing, the measurement of the level of accumulation of pro-inflammatory factors can serve as a valuable diagnostic tool, and the determination of the local concentration of inflammation control factors in the contents of periodontal pockets and tissue samples, and not in blood and other biological fluids that do not have direct contact with the focus, is especially informative. Particular emphasis in the review is placed on the ratio of the periodontal status of patients (pocket depth) and the concentration of such inflammatory signaling factors as TNFa and IL6.
In an article by Swiss and German authors PR Schmidlin et al. (2015) presents the results of a study of the contents of periodontal pockets by PCR with electrophoretic detection. The authors identified the 4 most dangerous periodontal pathogens and eight less dangerous bacteria (opportunistic periodontal pathogens - OP), and also evaluated their relationship with the state of periodontal tissues and MMP8 activity in saliva. OPs were found in dental plaque in 80% of cases. Active content MMP8 in saliva reached a critical value of over 40 ng/mL in saliva in 6 patients [211].
In the work of Finnish authors A. Salminen et al. (2014) showed that high levels of MMP8, ILip, and P. gingivalis in saliva are statistically associated with greater pocket depth and greater bone loss. At the same time, elevated concentrations of MMP8 and ILip were observed in patients with bleeding gums. The authors believe that the content of MMP8, ILip and P. gingivalis in saliva undoubtedly correlates with the data of clinical examination and X-ray examination of patients with periodontitis [27].
JM Leppilahti et al. (2015) studied 58 samples of gingival fluid/exudate obtained from volunteers: healthy individuals, patients with gingivitis and chronic periodontitis. When studying the local levels of nonspecific protection factors, it was found that the content of MMP8, MMP13, MMP14, myeloperoxidase and azurocidin is significantly higher in periodontitis than in gingivitis and intact periodontium ($p < 0.05$). The content of myeloperoxidase and MMP8 in patients with periodontitis strongly correlated ($r=0.95$, $p<0.0001$). It has been shown that the levels of all studied substances can be used in assessing the severity of the lesion with high diagnostic accuracy (>0.90), but only the content of MMP8 and myeloperoxidase can distinguish between foci of periodontitis and foci of gingivitis [17].
In the work of American authors JS Kinney et al. (2014) studied the diagnostic value of various biomarkers. The study involved 100 patients who were divided into 4 groups according to the state of periodontal tissues. The contents of MMP8, MMP9, osteoprotegerin, C-reactive protein, and ILip were determined in periodontal washings using ELISA. With the exception of C-reactive protein, all biomarkers showed significantly higher values in patients with CGP compared with the control group. Cluster analysis showed that the most accurate prediction (75% confidence) can be obtained by combining pathogen contamination and biomarker levels in periodontal washes (95% CI = 61.86) [14].
It is clear that the consequence of a phenomenon cannot manifest itself before the appearance of its cause. Using this principle, it is possible to significantly specify the role of signaling factors in the development and prevention of the disease [5]. In addition, only the analysis of the time dependence of changes in the concentration of factors makes it possible to predict the development of the disease, which is the main requirement of clinical diagnostic practice [8]. However, there are currently only a few publications in the literature on the dynamics of the synthesis of signaling factors, and they are limited to only two time points (usually before and after treatment).
In view of the foregoing, it can be concluded that at present there is an urgent need for a highly accurate and reliable method for detecting inflammatory periodontal diseases, which has the ability to track changes in the concentration of signaling factors over time [31]. The diagnostic systems obtained as a result of such studies will help to significantly reduce the level of errors in diagnosis, provide accurate prediction of the course of the disease and improve the quality of treatment.

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-19, February 2023
ISSN: 2749-3644

BIBLIOGRAPHY

1. Aimadinova, N.K. Early diagnosis of the development of periodontitis by determining prognostically significant RNA markers. / N.K. Aimadinova // Dentistry. - 2015. - No. 6. - T.94. - S. 54 - 55.
2. Aimadinova, N.K. The role of Prevotella intermedia in the course of chronic periodontitis, studied using real-time PCR / N.K. Aimadinova // VII Scientific-practical conference of young scientists "Fundamental and applied problems of dentistry and maxillofacial surgery". - Moscow, 2016.
3. Atrushkevich, V.G. Diagnosis and treatment of periodontal diseases in violation of mineral metabolism: Ph.D. dis. ... Dr. med. Sciences: 14.00.14. / Atrushkevich Victoria Gennadievna. - M., 2010. - 50 p.
4. Barer, G. The role of interferon and other cytokines in the occurrence and development of periodontal disease. / G. Barer, S. Grigoryan, N. Postnova // Cathedra. - 2006. - V. 5, No. 3. - S. 54-60.
5. Boriskina, O.A. Detection of prognostically significant molecular genetic markers for early high-precision diagnosis of the development of aggressive periodontitis: dis. ... cand. honey. Sciences: 14.00.14. / Boriskina Olga Andreevna. - M., 2014. - 146 p.
6. Ivanyushko, T.P. The study of opportunistic microorganisms by real-time PCR in patients with periodontitis. / T.P. Ivanyushko, L.V. Tumbinskaya, A.E. Donnikov // Dentistry. - 2011. - No. 5. - P.22-26.
7. Kozlov, S.A. Correction of the balance of the oral cavity as a condition for achieving an antiseptic effect in patients with inflammatory periodontal diseases. / S.A. Kozlov, A.N. Seleznev, L.N. Kolobkova and others // Bulletin of the Peoples' Friendship University of Russia. - 2007. - No. 2. - P.77-80.
8. Kofiadi, I.A. Methods detection oligonucleotide
9. polymorphisms: allele-specific PCR and hybridization with an oligonucleotide probe. / I.A. Kofiadi, D.V. Rebrikov // Genetics. - 2006. - V.42, No. 1. - P.22-32.
10. Tsepov, L.M. Factors of local resistance and immunological
11. oral reactivity. Methods for their clinical and laboratory assessment (literature review). 4.II. / L.M. Tsepov, L.Yu. Orekhova, A.I. Nikolaev and others //
12. Periodontology. - 2005. - No. 3 (36). - P.35-39.
13. Tsimbalistov, A.V. Features of the microflora of periodontal pockets in aggressive forms of periodontitis. / A.V. Tsimbalistov, T.T. Natsvlishvili, T.I. Kadurina and others // Institute of Dentistry. - 2010. - No. 4. - P.73-74.
14. Chepurkova, O.A. Features of microbiocenosis of the periodontal pocket in generalized periodontitis of moderate severity. / O.A. Chepurkova, M.G. Chesnokova, V.B. Nedoseko // Institute of Dentistry. - 2007. - No. 3. - P.86-88.
15. Amano, A. Variations of Porphyromonas gingivalis fimbriae in relation to microbial pathogenesis. / A. Amano, L. Nakagawa, N. Okahashi et al. // J. Periodont. Res. - 2004. - Vol.39. - P.136-142.
16. Anovazzi, G. Interleukin 4 haplotypes of susceptibility to chronic periodontitis are associated with IL-4 protein levels but not with clinical outcomes of periodontal therapy. / G. Anovazzi, LS Finoti, SC Corbi et al. // Hum. Immunol. - 2013. - Vol.74(12). - P.1688-95.
17. Bourmenskaya, O. Host gene expression profiling of cervical smear is eligible for cancer risk evaluation. / O. Bourmenskaya, E. Shubina, D. Trofimov et al. // J. Clin. Pathol. - 2013. - Vol.66 (4). - P.282-285.
18. Braga, RR Quantification of five putative periodontal pathogens in female patients with and without chronic periodontitis by real-time polymerase chain reaction. / RR Braga, MA Carvalho, O. Bruna-Romero et al. // Anaerobe. - 2010. - Vol.16(3). - P.234-239.
19. Burke, W. Genomics as a probe for disease biology. / W. Burke // New Engl. J. Med. 2003. - Vol.349. - P.969-974.
20. Cao, Z. Association of matrix metalloproteinase-1 promoter polymorphism with generalized aggressive periodontitis in a Chinese population. / Z. Cao, C. Li, L. Jin et al. // J. Periodontal. Res. - 2005. - Vol. 40(6). - P.427-431.
21. Chung, CH Molecular portraits and the family tree of cancer. /
22. H. Chung, PS Bernard, CM Perou // Nat. Genet. - 2002. - Vol.32(Suppl). - P.533540.
23. Cirelli, JA AAV2/1-TNFR:Fc gene delivery prevents periodontal disease progression. / Cirelli JA, Park CH, MacKool K. et al. // Gene Ther. - 2009. - Vol.16(3). - P.426-36.
24. Colombo, AV Identification of intracellular oral species within human crevicular epithelial cells from subjects with chronic periodontitis by fluorescence in situ hybridization. / AV Colombo, CM da Silva, A. Haffajee et al. // J. Periodontal. Res. - 2007. - Vol. 42. - P. 236-243.
25. Colonel, V. Gene expression profiling of 12633

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-19, February 2023
ISSN: 2749-3644

genes in Alzheimer hippocampal CA1: transcription and neurotrophic factor down-regulation and upregulation of apoptotic and pro-inflammatory signaling. / V. Colonel, J. Schurr, MJ Ball et al. // J. Neurosci. Res. - 2002. - Vol.70. - P.462-473.
26. Corbi, SC Clinical outcomes of periodontal therapy are not influenced by the ATC/TTC haplotype in the IL8 gene. / SC Corbi, LS Finoti, G. Anovazzi et al. // J. Periodontal Res. - 2014. - Vol. 49(4). - P.489-98.
27. Elamine, A. Prevalence of Aggregatibacter actinomycetemcomitans in Sudanese patients with aggressive periodontitis: a case-control study. / A. Elamine, JM Albandar, K. Poulsen et al. // J. Periodontal. Res. - 2011. - Vol.46(3). - P.285-91.
28. Hyvarinen, K. Detection and quantification of five major periodontal pathogens by single copy gene-based real-time PCR. / K. Hyvarinen, S. Laitinen,
29. S. Paju et al. // Innate immunity. - 2009. - Vol.15(4). - P.195-204.
30. Ianni, M. Variations in inflammatory genes are associated with periodontitis. / M. Ianni, G. Bruzzesi, D. Pugliese et al. // Immun. Aging. - 2013. - Vol.10(1). - P.39.
31. Inagaki, S. Porphyromonas gingivalis vesicles enhance attachment, and the leucine-rich repeat BspA protein is required for invasion of epithelial cells by "Tannerella forsythia" / S. Inagaki, S. Onishi, HK Kuramitsu, A. Sharma // Infect. Immun. - 2006. - Vol.74(9). - P.5023-5028.
32. Inagaki, S. Treponema denticola invasion into human gingival epithelial cells. / S. Inagaki, R. Kimizuka, E. Kokubu et al. // Microb. Pathog. 2016 Jan 22. pii: S0882-4010(16)00008-5. doi: 10.1016/j.micpath.2016.01.010.
33. Irshad, M. Cytokine and matrix metalloproteinase expression in fibroblasts from peri-implantitis lesions in response to viable Porphyromonas gingivalis. / M. Irshad, N. Scheres, D. Anssari Moin et al. // J. Periodontal Res. - 2013. - Vol.48(5). - P. 647-656.
34. Itagaki, M. Matrix metalloproteinase-1 and -3 gene promoter polymorphisms in Japanese patients with periodontitis. / M. Itagaki, T. Kubota, H. Tai et al. // J. Clin. Periodontol. - 2004. - Vol. 31. - P. 764-769.
35. Izuhara, K. Microarray-based identification of novel biomarkers in asthma. / K. Izuhara, H. Saito // Allergol Int. - 2006. - Vol.55. - P.361-367.
36. Javed, F. Cytokine profile in the gingival crevicular fluid of rheumatoid arthritis patients with chronic periodontitis. / F. Javed, HB Ahmed, T. Mikami et al. // J. Investig. Clin. Dent. - 2014a. - Vol. 5(1). - P.1-8.
37. Zhou, Q. Cytokine profiling of macrophages exposed to Porphyromonas gingivalis, its lipopolysaccharide, or its FimA protein. / Q. Zhou, T. Daste, M. Fenton et al. // Infect. Immun. - 2005. - Vol.73. - P.935-943.
38. Zorina, OA Analysis of the relationship of allele frequencies of the risk of aggressive periodontitis. / OA Zorina, OA Boriskina, NK Aymadinova, DV Rebrikov // The Way of Science. - 2014. - No. 6 (94). - R. 184-189.
39. Zorina, OA The relationship of genetic polymorphisms with the development of aggressive periodontites. / OA Zorina, OA Boriskina, NK Aymadinova, DV Rebrikov // Proceedings of the I International Scientific Conference "Global Science and Innovation". - Chicago, USA. - 2013. - R. 387-392