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Predicting the Course of Chronic Generalized Periodontitis

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Annotation. A large number and variety of works on the study of genes, controlling the activity of cytokines, confirms the relevance and the prospects of this direction in identifying predisposition, study of the mechanisms of development and course of periodontal diseases. It is known that the effect of cytokines on target cells in tissues periodontal can determine the features of the histopathological picture. The most important properties of IL-1 - stimulation of proliferation antigen-preactivated mature T-lymphocytes, increased production IL-2, IL-4, TNFα, stimulation of phagocytosis - well known and widely highlighted in the literature. The main cells producing IL-1, TNFα, IL-4 in the body are monocytes / macrophages, as well as T- and B-lymphocytes, neutrophilic leukocytes, endothelial cells.

Keywords. Intestinal microflora, IL-1, TNF-α, PGE-2, Oral mucosa.

There is evidence that the level of IL-1β correlates with the density location of macrophages and lymphocytes in inflammatory infiltrates. One of the first convincing evidence of the important role response of the host organism in the progression of periodontal destruction was work done on beagle dogs using flurbiprofen (a potent cyclooxygenase inhibitor), which reduced the degree of bone loss caused by periodontitis. Relationship the nature of structural changes in the periodontium and gene polymorphism controlling the production of cytokines have been evaluated in a number of studies.

At analysis of the distribution of IL-1β in the tissues of the gingival mucosa in the lesions maximum destruction near deep periodontal pockets was found that in the cell infiltrate was determined by the maximum the number of polymorphonuclear neutrophilic leukocytes and monocytic macrophage cells (CD68 positive). When evaluating the level of products IL-1β in these sites, the maximum values were obtained, compared with sites with less pronounced tissue destruction. Correlation analysis showed the presence of a strong positive relationship between the level of cytokine in tissue and density and composition of the cellular inflammatory infiltrate. Mechanisms of formation of inflammatory infiltrate in periodontitis is quite widely covered in the literature, back in 1976 (Page and Schroeder) and later in 1997 (Kornman) described the stages of formation changes in the epithelium and connective tissue of the gums with progression inflammation.

Already in the initial stages of inflammation, lymphocytes and neutrophilic leukocytes are the predominant cells fibroblasts begin to show signs of degeneration by apoptosis, collagen fibers are changed to provide space for leukocyte infiltration. Basal layer of epithelial cells proliferates to increase the physical barrier between the biofilm and connective tissue, acanthosis is formed. However, this early damage can persist for a long period of time, before more pronounced changes are formed, which depends on many factors, mostly related to host susceptibility.

However, it has been shown that teeth in a site of persistent inflammation demonstrated a 50-year survival rate of 63.4%, compared with 99.5% survival of teeth without inflammation. There are data that in younger individuals, the cellular infiltrate is dominated by lymphocytes, while at a later age the dominant type cell is plasma cells. Collagen degradation continues, while the infiltrate of inflammatory cells expands deep into the tissue, which accompanied by severe acanthosis. Impaired attachment of the epithelium allows deeper migration of the bacterial biofilm. This stage periodontal tissue lesions can also remain stable for several months or years, or may become more destructive lesions. Increasing infiltration by inflammatory cells, mainly plasma cells, extends deeply into the connective tissue, which leads to an increase in inflammatory changes and immunopathological tissue damage. main goal formation of the immune response of the host organism is protection from pathogen invasion, in periodontitis, as in some other chronic diseases, this reaction becomes part of the problem, as a variety of factors contribute to the maintenance of inflammation and destruction of periodontal tissues.

In addition to leukocytes and inflammatory lymphocytes infiltrate, periodontal cells, including fibroblasts, epithelial, endothelial cells become sources of biologically active agents such as IL-1, TNF-α, PGE-2 and participants in tissue destruction. It is assumed that the progression of the disease is due to a

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combination of many factors, in the presence of periodontopathogenic bacteria, high levels of pro-inflammatory cytokines, matrix metalloproteinases (MMPs), PGE-2 and low levels of interleukin-10 (IL-10), transforming growth factor-β (TGF-β) and tissue inhibitors metalloproteinases (TIMPs). In this concept, it is clear that the balance of cytokines determines what is happening - tissue destruction or homeostasis supporte.

Periodontal disease is associated with a higher proportion of anaerobic and Gram-negative bacteria such as Prevotella, Leptotrichia, Veillonella, Porphyromonas and Treponema. These bacteria can cause tissue destruction directly through endotoxins and enzymes or cause unbalanced immune response. In addition, a large number of studies have shown that inhibition of IL-1 and TNF-α decreases the recruitment of inflammatory cells (especially monocytes and lymphocytes) in periodontal tissue. As a result what causes a decrease in the severity of inflammatory changes in tissues, loss of attachment of gum tissues to the tooth and resorption bone tissue. Later, experimental studies in knockout mouse models supported the hypothesis that cytokines are the most important participants in the process of emergence, development and disease progression.

An important step in understanding the mechanisms of development and activation components of the host response was the study of the family of Toll-like receptors (TLRs), which are the first to detect the presence bacteria. Activation of the innate immune response occurs when binding of various bacterial components (diacyl peroxides, lipopeptides, peptidoglycan, lipopolysaccharides, flagellin, bacterial DNA) with TLRs, as a result of which intracellular signaling cascades leading to the activation of transcription factors such as nuclear factor-kB (NF-kB), protein activator-1 (AP-1), and p38 starting production various cytokines, many of which directly or indirectly stimulate the formation and activation of osteoclasts. Lymphocytes are present in large numbers in cell infiltrates of the gingival mucosa, are important immune cells that produce IL-1β, -6, -17, a receptor activator from NF-kB ligand (RANKL), TNF-α cytokines are among the best known factors associated with the destruction of periodontal tissues. Lymphocytes also secrete molecules that directly inhibit the formation osteoclasts, including osteoprotegerin (OPG); IL-4, -10, -13 and interferon-γ (IFN-γ). There is currently an opinion that both T and B cell populations are present in tissues periodontal disease progression, so it is reported that T and B cells, isolated from the tissues of the gums of patients with periodontitis, are more advanced stage of the cell cycle than peripheral T and B cells blood, demonstrating the activation of these cells directly in the tissues gums. In a pilot study immunodeficient (deprived of B and T-lymphocytes) and immunocompetent mice were infected with P. gingivalis, then observed significantly less bone destruction in the group of immunodeficient mice compared with immunocompetent mice, after which the authors concluded that B and T-lymphocytes, protecting the host from P. Gingivalis, contribute to significant bone loss when present. In another study, to detect cells that are source of an increased amount of RANKL in the presence of severe resorption of the supporting alveolar bone, the authors measured the concentration soluble RANKL in homogenates of affected tissues and found that RANKL concentrations were significantly higher in affected gingival tissues compared to healthy tissues. In affected gingival tissues, 50% of T cells and 90% of B cells were sources of RANKL, compared with 20% from B cells and T cells that expressed RANKL in healthy tissues gums. In addition, lymphocytes isolated from the gum tissues of patients with severe bone destruction, in vitro induce differentiation mature osteoclast cells in a RANKL-dependent manner, which may serve evidence that the source of RANKL for bone resorption may serve as activated T cells from gingival inflammatory infiltrate.

A similar study examined activated B cells, A. actinomycetemcomitans – immunized animals and it was shown that B cells from A. actinomycetemcomitans immunized animals had higher expression levels RANKL and caused a significantly higher level of differentiation osteoclasts than B cells of non-immune animals. Also immunized animals showed increased production osteoclasts on the alveolar surface of the bone, significant resorption alveolar. The study showed that B-lymphocytes can contribute to increased destruction of the connective tissue of the gums and bone resorption and this effect is associated with increased expression of RANKL. A serious contribution to the pathogenesis of resorption of the supporting alveolar bones introduces an autoimmune component associated with a response to damage to collagen type I, one of the main components of the periodontium.

It has been established that patients with periodontitis have higher anti-collagen type I antibody titers in gingiva compared to data level antibodies in peripheral blood. In addition, patients with periodontitis in the gum tissue in the inflammatory infiltrate clones of T-cells specific for type I collagen have been identified. It

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has also been shown in periodontal lesions to increase the number of autoreactive B cells expressing CD5+, producing a large amount of IgM and IgG to collagen than CD5-B cells in vitro.

It is known that the CD5+ molecule takes part in the modulation of signals, is also a dual receptor that is capable of both stimulating, and inhibit signals, on the surface of B - cells, is expressed only in response to very strong stimuli and the degree of CD5 expression indirectly epends on IL-1β. Although all the mechanisms that cause an immune response on the components of their own tissues, are not fully elucidated, the authors suggested that this mechanism explains the relationship between bacterial infection and subsequent autoimmune mechanisms of destruction tissues. Currently, there is an opinion that during the chronic phase lymphocytes perform a protective function, facilitating elimination of bacteria, delaying the progression of the disease. AT studies in normal rats infected with Actinomyces viscosus and Bacteroides gingivalis with B-lymphocyte depletion and reduced production antibodies showed a significant increase in bone loss alveolar bone. In an experimental study, serum blood from patients with severe periodontitis containing high titers antibodies to P. gingivalis, completely blocked bone resorption, and with the help of sera of people with low titers of these antibodies could not be stopped bone resorption. At the same time, the levels of antibodies to microorganisms of dental plaque positively correlates with periodontal destruction and bone loss, and it has even been suggested use these indicators to predict bone loss in the elderly patients.

These and other results indicate that specific antibodies produced in response to periodontopathogenic bacteria are protective but susceptible to facial periodontitis characterized by the production of antibodies that do not have protective properties. An important role in determining the effect of T-cell immune responses CD4+ T cells play against pathogens. Effector CD4+ T cells are divided into Th1 and Th2 subsets. Cytokines produced by Th1- lymphocytes include IFN-γ and TNF-α and -β, are critical for destruction of intracellular pathogens, but through direct or indirect influences realize the proresorptive effect. While Th2 cytokines IL-4 and IL-10 do not show such properties. Transplantation of antigen-specific Th1 cells into recipient rats and mice resulted in increased bone loss in animals stimulated by bacteria.

In contrast, rats and mice treated with Th2 cells demonstrated significantly less bone loss. These studies show that Th2 cells mediate production of specific antibodies, which is a key feature protection against periodontal destruction. There is evidence that during the transition from gingivitis to periodontitis and with the progression of periodontitis in the inflammatory infiltrate there is a change in populations of lymphocytes from prevailing in gingivitis of T-cells to an increase in the proportion of B-cells in the transition to periodontitis. And some authors suggest that susceptibility to progression diseases may involve predominantly Th2 cells producing cytokines necessary for the proliferation of B cell differentiation, which leads to the activation of polyclonal B cells that produce high levels of non-protective antibodies, as well as an increase in B-cell production IL-1β. Protects the periodontium from bacterial penetration predominantly activation of Th1 T cells, activation of innate immunity, and, if necessary, the production of protective antibodies.

Neutrophilic leukocytes are also abundant in cellular infiltrates in periodontitis and have both protective and destructive properties [294]. In the gingival sulcus, neutrophilic leukocytes form a barrier between the epithelium and plaque, which in normal can prevent bacterial invasion of the epithelium and underlying connective tissue [23, 125]. It is known that people with disorders of the functions of neutrophilic leukocytes, such as cyclic neutropenia, Chediak-Higashi syndrome, and adhesion deficiency syndrome leukocytes show an increased susceptibility to periodontitis. It was noted that in patients with refractory periodontitis, due to a decrease in rates of adhesion and opsonization by neutrophilic leukocytes, significantly phagocytosis is impaired compared to healthy patients. 70% patients with early aggressive forms of periodontitis are found dysfunction of neutrophilic leukocytes associated with chemotaxis and phagocytosis. But many researchers who paid great attention to attention to the analysis of families with various manifestations of early aggressive forms of periodontitis, did not find clear correlations with functional defects in neutrophilic leukocytes, which allowed them to read data violations of facultative risk factors for the development of early forms periodontitis.

There are several other concepts that explain the nature unbalanced host response to bacteria and their derivatives, in which discusses not hypoactivity, but hyperactivity of neutrophils leukocytes, which is accompanied by excessive release of toxic products by these cells and at least partly explains destruction of periodontal tissues. Respiratory burst is an important pathway for the destruction of microbes and includes the generation of superoxide, hydrogen peroxide, hydroxyl radicals and, subsequently, hypochlorous acid and

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chloramines. These enzymes are responsible for oxidative destruction of bacteria within the phagosome and can be released into the extracellular microenvironment, increasing oxidative stress directly in the connective tissue of the gums. Along with elevated levels of pro-inflammatory cytokines, foods accumulated as a result of oxidative stress in the immediate proximity to the alveolar bone, through the activation of various signaling pathways include RANKL-mediated alveolar bone resorption.

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