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The role of inflammatory mediators in the pathogenesis of dental inflammatory processes

Recent studies have proved that immunologic reactions are an intermediary mechanism in pulp diseases, periapical tissues inflammation, and parodontitis. However, these reactions are not limited only to inflamed tissues since antigens present in root canals and periapical tissues, and inflammatory mediators such as e.g. cytokines, leukotriens, prostaglandins, produced by stimulated lymphocytes, monocytes, macrophages, fibroblasts, osteoblasts, osteoclasts, induce significant changes in remote tissues and body organs, simultaneously taking part in systemic reactions, which also include the acute phase response (8, 13, 15).

In chronic inflammation of dental periapical tissues and parodontitis there is an increased amount of inflammatory mediators, and also a rise in the level of the acute phase factors in the blood serum, which play a key role in the pathogenesis of pulp diseases, periapical tissues diseases, and bone destruction which is usually associated with such diseases.

Bando et al. (2), Donoff et al. (4), and Meghjii et al. (12, 13, 14) on the basis of their studies, confirm the role of cytokines, collagenase, prostaglandins, leukotriens and eikozanoids in the inflammatory process (root cysts). Prostaglandins, leukotriens and eikozanoids, biologically active components of cell membranes, regulate the activity of adenyl cyclase, speed of cAMP synthesis and activity of protein kinases. In addition they are inflammatory reaction mediators, i.e. they increase venous micro vessels permeability, which leads to exudation, and they also have a chemotactic effect on leucocytes, attracting them to the focus of inflammation.

In dental granulomas Artese et al. (1) identified cells producing two types of cytokines: IL-1 beta and TNF-alfa. The small number of such cells, mainly macrophages and lymphocytes, is associated with – according to the authors – limited bone resorption observed in dental granulomas (5). The presence of TNF in periapical inflammatory exudates was also detected (5). The analysis of T cells in dental granulomas indicates that $CD4^+$ (T_H) cells are located in their central part, $CD8^+$ (T_S/T_C) cells, however, on their perimeters, nevertheless $CD4^+$ (T_H) cells play the most crucial role in the induction of accumulation and activation of other lymphocytes and macrophages. The authors also made observations which imply the presence of low concentrations of C-reactive protein in gangrenous pulp, they also suggested that the presence of CRP may facilitate pulp reparation processes. Ebersole et al. (6, 7) found that IL-2 levels were lower in healthy tissues than in tissues affected by recurrent parodontitis, and in the case of apical granuloma IL-2 production was, according to the authors, limited to small populations of T cells and mast cells.

Similarly, in the case of dental granuloma McNicholas et al. (10) discovered the presence of TNF-alfa (tumor necrosis factor performs immuno-modulating function, it is a pyrogen, stimulates

bone reconstruction by activating osteoclasts with the participation of Il-1), PGE_2, IL-1beta, IL-1alfa (interleukin-1 indirectly influences the hematopoietic system inducing the production of factors stimulating the growth of G-CSF, GM-CSF colonies, tumor necrosis factor, IL-2 and IL-6). Thus, having confirmed the conclusion presented by Donoff (4) in 1972, that suggested the interaction of cyst epithelium cells producing IL-1 and IL-2 (2, 11, 12, 13, 14) with cyst connective tissue fibroblasts (2), the authors simultaneously complemented their hypothesis with the role of epidermal growth factor (EGF) and fibroblast growth factor (FGF) in that interaction.

All types of dental cysts contain prostaglandins, leukotriens, IL-1 and IL-6 (2, 3, 12, 20, 31). Interleukin-6, whose production is stimulated by endotoxins, is produced in the focus of inflammation by monocytes, macrophages, eosinophils, fibroblasts, endothelial cells, and also B and T lymphocytes. It intensifies the production of the acute phase proteins by means of hepatocyte stimulating factor (HSF), a protein which is very similar to IL-6 in terms of structure and biological characteristics, which binds to receptors on hepatocytes surface and initiates the interactions of nuclear proteins with the gene regulatory sequences which are specific to the acute phase proteins. The basic function of IL-6 is activating the process of lymphocytes B differentiation into plasmacytes. The *in vitro* tests have shown that this cytokine plays an important role in the initiation of the acute phase response and intensifies the secretion of the following classes of antibodies: IgM. IgG and IgA. High concentrations of interleukin-6 activate mature osteoclasts, and also influence T lymphocytes by inducing the synthesis of the receptor for IL-2 and stimulating the interleukin secretion; IL-6 secretion by different types of cells may prove significant in various ways in the succeeding phases of immune response. An increase in IgM concentration (antibodies of that class are synthesized in the initial phase of immune response and released among the first ones, due to their great avidness they bind to antigen very effectively and activate the complement approx. 100–400 times more effectively than IgG), as well as the positive result of the rosette test (used to identify T lymphocytes because of their ability of spontaneous rosette formation with sheep erythrocytes) signify the effects of local immune responses taking place in periapical lesions, including cellular and humoral immune responses (2). Especially the second observation may prove interesting due to the fact that approx. 10% of the total T-lymphocyte pool penetrate periapical lesions. The complement system together with phagocytes, being the oldest and major element of nonspecific immune monitoring mechanisms, appears to play an important role in fighting dental inflammatory diseases. Marton et al. noted a considerable increase of the complement activity in the serum during 3-month observation, which implies that the concentration and complement cascade stabilization in periapical infections have considerable biological significance. The serum levels of five out of the six examined acute phase proteins were elevated in patients with untreated apical granulomas.

Concentration levels of E_2 prostaglandins were higher in acute and chronic inflammatory processes of periapical tissues compared to PGE_2 concentration levels observed in patients with healthy periapical tissues (considerably higher E_2 levels were observed more frequently in patients with acute inflammation than in the ones with chronic inflammation) (10). It has turned out that, e.g. all dental cysts and periapical granulomas (10) are able to synthesize prostaglandins. These results suggest a crucial role of E_2 prostaglandins in the pathogenesis of acute inflammatory processes of periapical tissues (10).

Inflamed dental cysts are one of the most common pulp gangrene complications. At present the dominant opinion is that the major inductor of the forming of cystomatous inflammatory foci are bacterial endotoxins found in the pulp as well as in periapical granulomas by Dahlen and Bergenholtz (3), Schein and Schider (15). Bacterial endotoxins are biologically active substances which have a mitogen effect on epithelium cells (12, 13) and induce production of cytokines in fibroblasts of surrounding connective tissue and the cells which take part in the inflammatory process (macrophages,

neutrophylic granulocytes, lymphocytes) (12). What is important is that in the inflammatory process periapical changes are accompanied by the activation of osteoclasts by paracrinely-secreted cytokines and inflammatory mediators, which leads to the bone resorption (2, 8, 9, 13).

Bacterial endotoxins from the root canal, which contains infected dead or gangrenous pulp, induce the inflammatory cascade and its indirect effects (activation of lymphocytes, monocytes and fibroblasts, production of cytokines and growth factors, secretion and/or release of prostaglandins, leukotriens, collagenase). The final effect of the inflammatory process is activating of osteoclasts which cause bone tissue resorption (3, 13, 15).

The immune system, responsible for defense, homeostasis and monitoring, performs its functions by means of numerous cells which are diversified morphologically and functionally. Each of the immune system tasks requires certain differences, which is reflected in the formation of the multiplicity of detector and effector mechanisms used by the system. For this reason the functional classification of immune response has been introduced which includes: non-specific, specific, humoral, cellular immunity. Each of these phenomena is accompanied by numerous reactions and interactions with the vascular system, especially with the endothelium, thrombocytes and erythrocytes equipped with C3bR receptor. The biological sense of the complexity of the immune response mechanism appears to be related to the necessity of selecting the most appropriate effector mechanism out of all the possible mechanisms. This complex strategy of the formation of an appropriate immune response is the result of co-operation of each of the elements of the immune system, which are in the state of dynamic equilibrium of autoregulatory relations in the immune system, as well as other relations which are external to the system and closely associated with the functions of the central nervous and endocrine systems. In recent years the term of immunoregulation has been created, which can be defined as the process deciding about specificity, direction, intensity and duration of the immune response (2, 6).

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SUMMARY

The authors present a review of the literature regarding function of inflammatory mediators in pathogenesis of periapical tissues inflammation. Immunologic reactions are an intermediary mechanism in pulp diseases and periapical tissues inflammation. There is an increased amount of inflammatory mediators such as cytokins- Il-1, Il-6, TNF alfa, collagenase, prostaglandin, leukotriens and CRP in inflamed periapical tissues.

Rola mediatorów reakcji zapalnych w patogenezie zębopochodnych procesów zapalnych

Autorzy prezentują przegląd światowej literatury dotyczącej roli mediatorów zapalnych w patogenezie stanów zapalnych tkanek okołowierzchołkowych. Reakcje immunologiczne są mechanizmami pośredniczącymi w chorobach miazgi i tkanek okołowierzchołkowych. W objętych procesem zapalnym tkankach okołowierzchołkowych stwierdzono zwiększoną zawartość mediatorów zapalnych, takich jak: cytokiny-Il-1, Il-6, TNF alfa, kolagenazy, prostaglandyny, leukotrieny, CRP.