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THE ROLE OF IMMUNE LINK IN THE PATHOGENESIS OF INFLAMMATORY PROCESSES IN THE PERIODONTIUM

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Inflammatory periodontal diseases are an important and actual problem in dentistry, among which the leading place is occupied by generalized periodontitis – the most severe lesion of periodons, which is characterized by a massive prevalence in the population.

The aim of the work was to investigate, based on a review of literary sources, modern views on the role of the immune system and its humoral link in the pathogenesis of inflammatory processes in the periodontium.

Materials and methods. A literature review was conducted using PubMed, Web of Science, SCOPUS, Google Scholar up to April 2024. There was no restriction on the date of publication or language.

Results and discussion.

During destructive-inflammatory processes in the periodontal complex, an increase in the level of immunoglobulins is observed, which is the result of pronounced antigenic stimulation with the spread of bacterial invasion under the gums. There is an active synthesis of antibodies followed by their transudation from the bloodstream into the gingival fluid. Violation of immune homeostasis observed in periodontitis is manifested by quantitative and qualitative changes in T- and B-lymphocytes, as well as increased synthesis of autoantibodies that initiate and maintain inflammation. Different types of white blood cells, known as leukocytes, actively contribute to the inflammatory process and tissue damage within the periodontal complex. Among these, key players include neutrophils, monocytes/macrophages, and lymphocytes. When activated by microorganisms, monocytes and macrophages produce a series of cytokines, triggering an imbalance between pro-inflammatory and anti-inflammatory responses. This imbalance ultimately leads to tissue resorption, as previously mentioned.

Conclusions. Immunopathological processes are of great importance in the formation and progression of inflammatory diseases of the periodontal complex, and their course depends on disorders in the specific and non-specific links of innate and adaptive immunity.

Key words: periodontitis, oral mucosa, cytokines, immunoglobulins, periodontal disease, immunity, neutrophils.

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РОЛЬ ІМУННОЇ ЛАНКИ В ПАТОГЕНЕЗІ ЗАПАЛЬНИХ ПРОЦЕСІВ У ПАРОДОНТІ
Тернопільський національний медичний університет імені І. Я. Горбачевського Міністерства охорони здоров'я України, Тернопіль, Україна

Захворювання пародонта характеризуються великим поширенням серед населення, незворотністю розвитку, прогресуючим перебігом запального процесу та можуть призвести до виникнення хронічної інфекції в організмі. Мета роботи – дослідити сучасні погляди на роль імунної системи та її гуморальної ланки в патогенезі запальних процесів у пародонті. У разі цих запально-деструктивних процесів спостерігається підвищення рівня імуноглобулінів, кількісні та якісні зміни Т- і В-лімфоцитів, посилення синтезу аутоантитіл, що ініціюють і підтримують запалення. Активовані мікроорганізмами моноцити та макрофаги синтезують каскад цитокінів, викликаючи дисбаланс між про- та протизапальним пулом. Імунопатологічні процеси мають вагоме значення у формуванні та прогресуванні запальних захворювань пародонта, їхній перебіг залежить від порушень у специфічній і неспецифічній ланках вродженого та адаптивного імунітету.

Ключові слова: пародонтит, слизова оболонка порожнини рота, цитокіни, імуноглобуліни, пародонт, імунітет, нейтрофіли.

Introduction. Periodontal disease is an important and urgent problem in dentistry [1]. In the general structure of periodontal diseases, a prominent place is occupied by generalized periodontitis (GP) – the most severe lesion of periodontal tissues, which is characterized by mass prevalence in the population, the occurrence of a focus of chronic infection in the body, the irreversibility of development, the progressive course, which ultimately leads to the loss of a significant number of teeth and disorders of the function of the maxillofacial system [2].

Modern research suggests that generalized periodontitis is a chronic inflammatory-dystrophic process resulting from various factors [3]. Etiological factors typically involve traumatic impacts from fixed orthopedic structures or removable dentures [4], deficiencies in dental fillings, carious lesions, dentition defects [5], occlusion abnormalities, prosthetic challenges [6], improper frenulum attachment, minor oral cavity anomalies, inadequate oral hygiene, as well as habits and other factors [7]. Among the prevalent causes of inflammatory periodontal diseases, key contributors include disruptions in immunological reactivity, medication use, environmental stressors, and more [8].

Chronic generalized periodontitis is a significant contributor to tooth loss, even occurring at a young age. It can result in alterations in the chewing apparatus, affecting facial aesthetics and speech function. Additionally, it can negatively impact the functioning of the digestive system and other bodily systems [9]. Extensive research has highlighted the strong association between periodontal pathology and systemic diseases, as evidenced by the high occurrence (74%) of other organ and system pathologies among patients with periodontitis [10; 11].

Presently, there is evidence highlighting the significance of immune dysregulation in the development of periodontitis, ultimately resulting in a chronic and recurrent condition [12]. In recent years, there have been publications about the immunopathological mechanisms of periodontal diseases [13]. Many researchers are unanimous in their opinion that immunopathological processes play a leading role in the emergence and development of generalized forms of periodontal diseases [3]. Violations of general and local immunity in inflammatory periodontal diseases were revealed [14].

The aim of the work was to investigate, based on a review of literary sources, modern views on the role of the immune system and its humoral link in the pathogenesis of inflammatory processes in the periodontium.

Material and methods. The literature review is grounded on the analysis of a significant volume of digital publications, which were found as a result of a literature search on global databases, such as PubMed (https://pubmed.ncbi.nlm.nih.gov), Web of Science Core Collection (https:// www.webofscience.com/wos/woscc/basic-search), Scopus (https://www.scopus.com) and Google Scholar (https://scholar.google.com.ua). A literature review was carried out to identify publications about the modern views on the role of the immune link in the pathogenesis of inflammatory processes in the periodontium, disruption of immune homeostasis in specific and non-specific links of innate and adaptive immunity, as well as cytokine profile. The bibliographic research was conducted between 20 October 2023 and 20 April 2024 to analyze the most recent evidence. We conducted searches utilizing MeSH (Medical Subject Headings) terms, employing synonyms and various combinations of the following search terms: “periodontitis”, “oral mucosa”, “cytokines”, “periodontal disease”, and “immunity”. In addition to the electronic search, an analogical search was carried out in the bibliographic references of the selected articles. In addition to the electronic search, a similar search was performed in the bibliographic references of the selected articles. A total of 62 sources of literature were selected and processed during the primary analysis, which included evidence-based randomized trials, systematic reviews, and others. After further systematization of the selected information using general scientific methods (analysis, synthesis, generalization, critical evaluation of the collected data), 46 most relevant sources remained. Exclusion criteria were publications that did not meet the purpose of this review, results, publication language other than English and Ukrainian. Methods used for design and writing of the article: bibliographic and analytical.

Results and discussion. It was established that as the pathological process in the periodontium progresses, there is a gradual decrease in non-specific protection, which subsequently leads to an increase in the activity of specific factors [15]. Humoral factors of adaptive immunity play a major role in the pathogenesis of chronic generalized periodontitis, first of all, immunoglobulins produced by plasma cells (activated B-lymphocytes) and are specific for a particular antigen [16]. Immunoglobulins of three classes associated with periodontal tissues are found most often in gingival fluid and blood serum: IgA, IgG and IgM [17]. During inflammatory and destructive processes in the periodontal complex, an increase in the level of immunoglobulins is observed, which is the result of pronounced antigenic stimulation with the spread of bacterial invasion into periodontal pockets and areas of tooth-gingival attachment. At the same time, there is an active synthesis of antibodies followed by their transudation from the bloodstream into the gingival fluid [15; 18]. Thus, factors of local immunity found in gingival fluid are also a manifestation of the general humoral link of adaptive immunity. That is, the gingival sulcus can be positioned as a kind of “representative” of general immune protection in the periodontal complex [3].

At the same time, a certain part of immunoglobulins is formed locally, in the tissues of the marginal periodontium, so the origin of these antibodies included in the inflammatory process has both a systemic and a local character [12; 19].

Elevated levels of IgA typically signify the presence of either an acute or chronic infection, including those of bacterial origin. Immunoglobulins of the M class primarily mediate antibacterial immunity and are the first to be synthesized in response to an infectious agent [20]. G immunoglobulins, on the other hand, serve as the primary effectors of the humoral arm of adaptive immunity. Studies have shown that the majority of antibodies targeting bacteria belong to the IgG class [21].

A high level of sIgA, IgG, and complement components is noted in the contents of periodontal pockets, provided the

inflammatory process develops and progresses [22]. When antibodies directly react with antigens, a cytotoxic response ensues, resulting in tissue structure destruction. Research has confirmed that the most commonly encountered cytotoxic antibodies are of the IgM and IgG classes [23].

Violation of immune homeostasis observed in periodontitis is manifested by quantitative and qualitative changes in T- and B-lymphocytes, as well as increased synthesis of autoantibodies that initiate and maintain inflammation [24].

It should be noted that changes in the circulatory system and microcirculation have a significant impact on the development and course of inflammation in the periodontium [9]. Leukocytes, as the main effector cells of inflammation, are actively involved in immune protection, and the entire blood complex contributes to the formation and maintenance of leukocyte infiltration, which is a key mechanism of inflammation [25].

Various phenotypes of leukocytes play an active role in the development of the inflammatory process and tissue destruction of the periodontal complex, the main ones of which are neutrophils, monocytes/macrophages and lymphocytes [26]. Neutrophils, which constitute a significant part of polymorphonuclear leukocytes or granulocytes, play a key role, as they are the first to respond to chemotactic factors released by dental plaque microorganisms [27]. In significant quantities, they infiltrate periodontal tissues and perform their main effector functions, including chemotaxis, adhesion, phagocytosis, "oxidative explosion" [28; 29]. The presence of a significant number of effector cells in the focus of infiltration, as well as their complex mechanisms of interaction and potentiation lead to the formation of a complex peculiar chronic dystrophic-inflammatory process [14].

At the same time, the existence of somatic pathology, which weakens the body's protective mechanisms, can contribute to the negative impact on the periodontal complex, both of the pathogenic microflora located in the oral cavity and endogenous periodontopathogenic factors [14; 30]. They are capable of autosensitization and the development of immunopathological processes. It follows that inflammatory periodontal diseases can be considered with confidence as diseases with etiological and pathogenetic systemic factors [31].

When the pro-inflammatory agent (antigen) persists without timely elimination, and the inflammation transitions into a chronic state, characterized by increased activity of anti-inflammatory factors, for example IL-10, a substantial destructive process ensues [32]. Consequently, monocytes and macrophages, activated by pathogenic microorganisms, produce a cascade of cytokines, disrupting the balance between pro- and anti-inflammatory responses, ultimately leading to tissue resorption [33]. This understanding forms the foundation of the cytokine concept regarding the development of chronic inflammation, including within the periodontal complex [34].

Among the cytokines, pro-inflammatory IL-1β and TNF-α have the most pronounced damaging properties for periodontal tissue [35]. Specifically, studies have demonstrated a direct correlation between the severity of periodontitis and the concentration of TNF-α in venous blood [36]. Additionally, IL-1β serves as one of the primary mediators facilitating the spread of the pathological process within the periodontium [37].

IL-1β is primarily produced by macrophages, with lesser contributions from dendritic cells, endothelial cells, and fibroblasts [38]. Its functions include stimulating the emigration of polymorphonuclear leukocytes from the bone marrow, inducing the exocytosis of lysosomal enzymes and free radicals by phagocytes, promoting degranulation of mast cells, activating prostacyclin production, stimulating the synthesis of acute phase proteins by hepatocytes, and eliciting a pyrogenic effect [39].

IL-1β and TNF-α exert their effects on bone tissue by stimulating the activation of osteoclasts, leading to bone resorption. They also hinder tissue repair processes by inhibiting the resynthesis of collagen fibers by fibroblasts and promoting the synthesis of collagenases. Notably, these activities are evident even at low concentrations of these cytokines [34].

It has been observed that as generalized periodontitis advances, there is a notable elevation in the levels of these cytokines both in gingival tissues and gingival fluid [40]. In cases where inflammatory processes within the periodontium become chronic, particularly common among elderly patients, there is an imbalance between cytokines, resulting in the hyperactivation of osteoclasts. Consequently, the extent of degenerative-destructive lesions in the alveolar bone in generalized periodontitis correlates directly with the accumulation of cytokines [41].

In addition, in the pathogenesis of periodontitis and bone resorption, a special role is played by the increased secretion of anti-inflammatory IL-10, which prevents the development of a full-fledged inflammatory reaction, the main task of which is the elimination of pathogenic [32]. As a result, a sluggish course of periodontitis is clinically observed against the background of pronounced destructive processes in the periodontal complex [23].

Cytokines are protein-peptide factors synthesized by various cells, mediating short-range regulation of intercellular and intersystem interactions [34]. While immune cells are primary cytokine producers, endothelial cells also contribute to cytokine production. Moreover, it has been observed that the same cytokine can be generated by cell types originating from different tissues and organs [36]. The functions of cytokines encompass regulating immune responses, inflammatory reactions, hematopoiesis, participation in apoptosis, angiogenesis, and facilitating chemotaxis [34].

Currently, the cytokine system comprises over 300 polypeptide substances [42]. Among them, the most extensively researched are cytokines of the immune system, which are secreted during the execution of both general and local immunity mechanisms, exhibiting activity even at extremely low concentrations [36]. These molecules can be regarded as mediators of inflammatory reactions with various types of regulation, including endocrine, paracrine, and autocrine [43].

In cytokine action mechanisms, phenomena like antagonism and synergism are observed, along with their interchangeability and pleiotropism. Antagonism refers to the ability of one cytokine to inhibit the actions of another, while synergism denotes the enhancement of effects when

multiple cytokines act together. Moreover, cytokines exhibit pleiotropic effects, meaning a single mediator can influence various processes and act on multiple cell types, inducing diverse effects [36].

Interleukins are of paramount clinical and immunological significance. These polypeptides can be classified based on their mechanism of action into three main categories: pro-inflammatory, anti-inflammatory, and regulatory interleukins with their own effector functions such as cytotoxic or antiviral activities. Pro-inflammatory interleukins induce inflammatory responses, while anti-inflammatory interleukins limit the progression of inflammation. Regulatory interleukins play a role in modulating immune responses and have diverse effector functions [44; 45].

The synthesis of cytokines experiences a sharp increase in response to tissue stress, making it an inducible process that is largely absent outside of inflammatory reactions and immune responses [46]. For instance, exposure to infectious agents, such as molecules like lipopolysaccharides, peptidoglycans, and muramyldipeptides found in the cell wall of gram-negative periodontopathogenic bacteria, triggers the activation of macrophages. This activation leads to heightened production of pro-inflammatory cytokines like IL-1β. These cytokines, circulating in the bloodstream, further stimulate the secretion of acute phase proteins [43].

As the dystrophic-inflammatory process progresses, there is typically a decrease in the level of nonspecific protection while the function of specific factors intensifies. In many instances, there is an elevation in the concentration of various serum immunoglobulins, although in some cases, their levels may remain unchanged or even decrease. Significant alterations in the immunological system are primarily observed in cases where the dystrophic-inflammatory process persists for an extended duration, eventually leading to the destruction of periodontal tissues.

Based on the current advancements in clinical immunology, it can be asserted that the cytokine profile of the blood holds significance in understanding the general immunopathogenesis of numerous chronic diseases, including those pertaining to dental health. Recent research has underscored the crucial role of cytokines in mediating intercellular interactions underlying the development of chronic inflammation within the periodontal complex. This includes elucidating the mechanisms of dystrophic-inflammatory lesions that may culminate in osteoporosis and the resorption of alveolar bone, ultimately resulting in compromised function or even teeth loss.

Cell-mediated immune reactions play a pivotal role in inducing cytotoxic effects on cells within the periodontal-pathogenic complex. These reactions significantly influence the level of inflammation activity and the resorption of interalveolar partitions. As primary factors of innate, nonspecific tissue protection, cell-mediated immune responses are essential for antimicrobial and anti-infective defence mechanisms. They represent an unstable equilibrium between two types of immune reactions, which can dynamically shift in various directions. This delicate balance determines the nature and severity of the inflammatory process within the periodontium.

Conclusions. Immunopathological processes play an important role in the formation and progression of generalized inflammatory periodontal diseases, the course of which depends on disorders in the specific and nonspecific system of innate and adaptive immunity, as well as changes in the cytokine profile. Violation of the humoral link of immunological reactivity in periodontitis is an essential pathogenetic link that shapes the nature of the development and dynamics of the inflammatory process.

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Declaration of Competing Interest.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical statement

All authors declare that ethical approval is not required for this review study.

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