SCHOLASTIC:
Journal of Natural and Medical Education
Volume 2, Issue 11, Year 2023 ISSN: 2835-303X
https://univerpubl.com/index.php/scholastic

CYTOKINE SYSTEM IN NORMAL AND IN RESPIRATORY ORGAN DISEASES

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Article Information

Received: Oct 25, 2023
Accepted: Nov 24, 2023
Published: Dec 1, 2023

Keywords
immunity, action of cytokines, inducibility, bronchial asthma, allergy.

ABSTRACT
The article reviews literature data on the problem of studying the activity of the cytokine system, which plays an important and diverse role in the development of immune, allergic and inflammatory reactions in respiratory diseases.

Introduction

Cytokines are non-antigen-specific proteins produced predominantly by activated cells of the immune system [25, 36]. Performing the functions of mediators of the immune system, they regulate the strength and duration of the immune response and the inflammatory process, providing intercellular interactions, positive and negative immunoregulation and are growth factors, differentiation of lymphoid and other cells [15]. Stimulators of cytokine formation can be biological, physical, or chemical stimuli. Depending on their nature, cytokines act autocrinely on the producing cells themselves, paracrinely on other target cells, or endocrinely on various cells outside the site of their production. The action of cytokines is carried out in very low concentrations (10-15 M) through high-affinity receptors on the surface of target cells. Cytokines are not isolated peptides, but an integral system, the main components of which are the producing cells, the cytokine protein itself, the receptor that perceives it, and the target cell. By

interacting with each other in an agonistic or antagonistic manner, they change the functional state of target cells and form a cytokine network. Their action is implemented according to the network principle, i.e. The information transmitted by the cell is contained not in one individual peptide, but in a set of regulatory cytokines [25, 36].

In recent years, it has become clear that the regulatory role of cytokines in the body is not limited only to the immune response and can be divided into four main components:

• Regulation of embryogenesis, formation and development of a number of organs, including organs of the immune system.

• Regulation of certain normal physiological functions, such as normal hematopoiesis.

• Regulation of the body's defense reactions at the local and systemic level.

• Regulation of regeneration processes to restore damaged tissues [36].

The cytokine system currently includes about 200 individual polypeptide substances. All of them have a number of common biochemical and functional characteristics, among which the most important are the following: pleiotropy and interchangeability of biological action, lack of antigen specificity, signal transmission through interaction with specific cellular receptors, formation of a cytokine network. In this regard, cytokines can be isolated into a new independent system for regulating body functions, existing along with nervous and hormonal regulation [36].

Within the immune system, cytokines mediate the relationship between nonspecific protective reactions and specific immunity, acting in both directions. An example of cytokine regulation of specific immunity is the differentiation and maintenance of balance between T-lymphocytes helper types 1 and 2 (Th1 and Th2). In case of failure of local protective reactions, cytokines enter the circulation, and their action is manifested at the systemic level, which leads to the development of an acute phase response at the body level. At the same time, cytokines influence almost all organs and systems involved in the regulation of homeostasis. The effect of cytokines on the central nervous system leads to changes in the entire complex of behavioral reactions, the synthesis of most hormones, acute-phase proteins in the liver, the expression of genes for growth and differentiation factors changes, and the ionic composition of the plasma changes. However, none of the changes that occur are of a random nature: all of them are either necessary for the direct activation of protective reactions, or are beneficial in terms of switching energy flows to combat the invading pathogen. At the body level, cytokines communicate between the immune, nervous, endocrine, hematopoietic and other systems and serve to involve them in the organization and regulation of a single protective reaction. Cytokines serve as the organizing system that forms and regulates the entire complex of pathophysiological changes during the introduction of pathogens [10, 31, 36].

Cytokines are regulators of the body’s defense reactions; they enhance the effector mechanisms of elimination of foreign antigens, regulate inflammation and regeneration [14]. The target cells for cytokines in allergies and infectious processes are mast cells, basophils, eosinophils, neutrophils, macrophages, T cells and B cells of the respiratory tract, and vascular endothelial cells. The same cytokine can be produced by different cells and affect the functions of cells of different types. A cascade of cytokines, differing in their mechanisms of influence on physiological functions, is involved in the development and course of the allergic and inflammatory process [31].

A number of cytokines have the ability to initiate and stimulate inflammatory responses (IL-1, IL-6, IL-8, IL-12, IL-16, IL-18, TNF-α, IFN-α, IFN-γ), while others suppress them (IL-4, IL-10, IL-13) [2, 37, 38]. Cytokines can exist not only in the form of circulating molecules, but also in

bound form (IL-1α, TNF-α). In general, cytokines are signaling molecules that play a key role in the immune system in health and disease [5, 31, 35, 36].

Cytokines include interferons (cytokines with antiviral activity), colony-stimulating factors, chemokines (chemotactic cytokines), transforming growth factors; tumor necrosis factor; interleukins (factors of interaction between leukocytes) with historically established serial numbers and some others [26, 35, 36].

Classification of cytokines can be carried out according to their biochemical and biological properties, according to the types of receptors through which cytokines carry out their biological functions, as well as a functional classification of cytokines [26, 35].

The most important principles of the cytokine system are:

Inducibility – cytokines should not be produced in a resting immune system. An increase in their activity is observed under the influence of external factors (microorganisms or specific antigens). The condition for the development of a cell response to the action of cytokines is the presence of a sufficient number of functioning receptors on their surface. On resting cells, their number is small and insufficient to ensure a response to the corresponding factor. Only very high doses of the cytokine can have an effect on a resting target cell. Usually, under the influence of an inducer, the number of receptors on the cell surface increases to the required level [26].

Redundancy – each type of immune system cell is capable of producing several cytokines and each type of cytokine can be secreted by different cells, and all cytokines are characterized by polyfunctionality with strong overlapping effects [26].

The interconnectedness and interaction of components - cytokines influence each other's production. More complex are the relationships between cytokines belonging to different groups of origin. The relationship between Th1 and Th2 types at the level of cytokine production is mutually inhibitory; they are mediated through IFN-γ and IL-10. Within the groups of lymphokines produced by Th1 and Th2 types, there are positive mutual influences, which is confirmed by the fact that growth factors for Th1 and Th2 types are their products (IL-2 and IL-4, respectively) [2, 5, 26].

In lung diseases, cytokines are involved in the infectious-inflammatory process and the allergic response at the level of the immune mechanisms themselves and the effector link, largely determining the direction, severity and outcome of the pathological process [25].

Allergic and non-allergic mechanisms can lead to similar changes, the most typical of which is infiltration of inflammatory cells (lymphoid cells, eosinophils, mast cells, etc.), thickening of the basement membrane of the mucous membrane, damage, desquamation of the epithelium.

During asthmatic inflammation, lymphocytes that control the production of antibodies produce regulatory factors that lead to the production of antibodies predominantly of the IgE class (IL-4, IL-13), attracting eosinophils to the site of inflammation and promoting their subsequent activation IL-5, GM-CSF, GCSF. Such lymphocytes are called Th2 lymphocytes, and the biologically active regulatory proteins they secrete (IL-4, IL-13, IL-5) give the Th2 cytokine profile [17, 28]. Mast cells and eosinophils involved in inflammation also secrete Th2 profile cytokines, inducing Th2 lymphocytes. Thus, a vicious circle is created that maintains the characteristic inflammation in the wall of the respiratory tract. Inflammatory changes are associated with bronchial hyperreactivity, a typical functional sign of bronchial asthma [6, 22, 23, 31].

Chronic obstructive pulmonary disease (COPD) is characterized by increased levels of IL-8 and IL-6 in sputum [12]. The direction of movement of neutrophils into the lesion is determined by

chemotractants, the most active of which is IL-8. A slight attraction of immune system cells to the site of inflammation due to low basal and stimulated levels of IL-8 in patients with COPD leads to chronic carriage of intracellular parasites and a constant sluggish infectious process that is difficult to respond to traditional etiotropic therapy, which contributes to the increase in all signs of the disease and the aggravation of bronchial obstruction [29].

COPD is 70% represented by obstructive bronchitis, and this category does not include non-obstructive forms of catarrhal and purulent bronchitis, which are no less relevant for many regions of Uzbekistan [1, 9].

According to a number of authors, the amount of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) in patients with chronic non-obstructive bronchitis significantly exceeds their levels in healthy people. This is especially true for IL-1, IL-2, and for the level of IL-4 - no significant changes were obtained [1].

The cytokine profile in patients with non-obstructive forms is directed towards Th1, in contrast to obstructive bronchitis [1].

Hyperinduction of TNF-α, IL-1α, IL-8 in patients with chronic obstructive bronchitis leads to the development of severe forms of the underlying disease [4, 12, 25, 29, 32]. There is a relationship between the level of cytokines and the duration of the disease and the severity of clinical manifestations. In patients with a history of chronic obstructive bronchitis of less than 5 years, pro-inflammatory cytokines (TNF and IL-6) and anti-inflammatory cytokines (IL-2 and IFN-γ) are lower than in patients with a longer history of the disease [1, 9, 19]. The level of IL-2, IFN-γ, IL-1β has a direct relationship with the severity of clinical manifestations during exacerbation of chronic bronchitis. No correlation was found between these indicators and IL-4 levels. A connection between smoking and impaired IL-4 production is possible, but this requires study. In the lavage of smokers, IL-4 is significantly reduced, but IL-8, IL-1β, and TNF-α are increased [1, 9].

Conclusion

The study of cytokines shows their significant and diverse role in the development of immune, allergic and inflammatory reactions in respiratory diseases. Emerging new data on the nature and functions of these mediators complement the understanding of the pathogenesis of pulmonary diseases. As the role of cytokines becomes clearer, it becomes possible to control the inflammatory process and other pathophysiological consequences of lung injury.

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