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THE ROLE OF MACROPHAGES AND CYTOKINES IN THE FORMATION OF INFLAMMATION AND PROGRESSION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract:

Recently, genetically engineered drugs have occupied a significant place in the list of promising medical drugs under development. The active ingredient of these drugs is genetically engineered drugs based on cytokines. The trend of using the transforming growth factor (TGF-β1) has appeared in recent years as an absolutely new trend in the system of medication correction of the inflammatory process course. The regulatory role of TGF-β1 in the evaluation of the direction of immune response has been shown. Much attention is paid to the role of TGF-β1 in the regulation of cell proliferation and differentiation in the body.

Keywords: Transforming Growth Factor, Cytokine, Inflammation.

OBJECTIVE OF THE REVIEW:

To consider some of the priority pathogenetic mechanisms involved in the formation of chronic obstructive pulmonary disease.

INTRODUCTION.

The study of chronic alveolar/bronchial inflammation is a key factor in the development of the theory of the pathogenesis of many pulmonary pathologies. Chronic obstructive pulmonary disease (COPD) is one of the most important problems of modern public health, and this is the case in almost all countries due to the ever increasing prevalence and mortality of this disease. COPD is the only disease from which deaths continue to increase. According to a study by the World Health Organisation and the World Bank, by 2020, COPD will account for 5 per cent of all deaths. COPD will be the 5th most common disease and the 3rd leading cause of death among all diseases.

Acute or chronic alveolar/bronchial inflammation is known to be a key factor in the pathogenesis of many pulmonary pathologies, such as bronchial asthma, COPD, adult respiratory distress syndrome and idiopathic pulmonary fibrosis. The localisation and specificity of the inflammatory response may be different for each of these diseases, but all are characterised by the involvement and activation of inflammatory cells in the lung tissue. These activated cells can produce cytokines, oxidants and many other mediators that are involved in inflammation [1-4].

The underlying pathogenesis of COPD is a chronic, diffuse, non-allergic inflammatory airway lesion, which involves neutrophils, with increased activity of myeloperoxidase, neutrophil elastase, and metalloproteinases. The inflammatory response is associated with neutrophil infiltration in the inflammatory focus, with increased activity of interleukins-6 and -8 and tumour necrosis factor-alpha (TNF-alpha) (5-7). The inflammatory process is multifactorial in nature and is a complex system of interaction between inflammatory cells, the cytokines and growth factors they produce, and the activation of the receptor response of each cell group involved in the inflammatory process. Increased sympathetic activity in COPD patients contributes to the activation of the renin-angiotensin-aldosterone system (RAAS) and other neurohormones and mediators (cytokines, endothelin, vasopressin, etc.) Nowadays, it is known that the unit of inflammation in COPD is small bronchi, bronchioles and acini, where as a result of inflammation of mucosal and submucosal layers thickening of bronchioles walls, hypertrophy of smooth muscles of these structures and involvement in the inflammation process of bronchiolar microenvironment, which potentiates development of vicious circle of inflammation, destruction of interalveolar membranes [8-13] develops. The involvement of phagocytic active cells - neutrophils, macrophages, immunocompetent cells, which are the main sources of inflammatory mediators, contributes to the persistence of inflammation [12]. The balance of the system of pro- and anti-inflammatory cytokines, growth factors regulating their production and interaction, as well as attracting new immunocompetent cells to the site of inflammation, determines the degree of transition of reversible airway obstruction into irreversible and,

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therefore, determines the severity of COPD course [7,14].

Cytokines are hormone-like proteins produced by various cells (lymphocytes, monocytes, granulocytes, mastocytes, endotheliocytes, fibroblasts, and other cells) with a wide spectrum of biological activity, which perform intercellular interaction in hematopoiesis, immune and inflammatory responses and intersystem interactions [15-18]. Cytokines are traditionally divided into interleukins (IL-1 - IL-15), tumor necrosis factors (TNF-alpha and -beta), migration inhibitory factor, interferons, chemotactic factors, growth factors (fibroblast growth factor, transforming growth factor - TGF-beta, epithelial and endothelial growth factors, etc.) [7,8,19,20].

Most pro-inflammatory cytokines are produced by neutrophils, activated lymphocytes, endothelial cells and smooth muscle cells. Normally, pro-inflammatory cytokines should not be in circulation, but in some cases they may appear as a manifestation of latent inflammatory processes, as well as of immunopathological conditions. TNF-alpha has a wide range of effects. Through TNF-mediated induction of growth factor genes, cytokines, transcription factors, receptors, mediators and acute inflammatory phase proteins, and pyrogens, it is involved in the induction of cachexia. There is experimental evidence that activation of cytokine system, mainly TNF-alpha production, is associated with high activity of SAS, RAAS and state of chronic hypoxia [13]. Increased activity of the neurohumoral system stimulates the production of cytokines that have proinflammatory effects, which determines the development of pathological changes. The leading role in the pathogenesis of inflammation in COPD is assigned to neutrophils. As the existing data show, in the regulation of neutrophil apoptosis, the balance between pro-inflammatory and anti-inflammatory cytokines is essential to ensure the timely removal of "excessive" granulocytes after their function in the inflammation focus. If neutrophil apoptosis is inhibited, however, there is a risk of persistence of inflammation in the surrounding tissues, as neutrophils aggressively produce inflammatory cytokines, which is observed in patients with septic diseases in studies of various apoptosis markers in bronchoalveolar lavage, in biopsies in bronchial mucosa and in blood . Three stages can be distinguished in the development and functioning of neutrophils, when the most significant differences in the readiness of cells to implement the process of apoptosis are observed: 1) maturation in bone marrow; 2) staying in circulation; 3) being in tissues, including exudative neutrophils (salivary, peritoneal, wound, intranasal, vaginal, bronchoalveolar) should be included here [22,23].

Thus, activation of cytokine system in COPD patients is a marker of disease progression with involvement of more and more new components in pathogenesis, including human neurohumoral system, leading to appearance and progression of LH, which requires special pharmacotherapeutic tactics in management of these patients [6].

The study of neutrophils in patients with severe septic diseases revealed an interesting fact - the presence of a high percentage of neutrophils (compared with healthy people) with a pronounced expression of CD95 (ARO-1, Fas) on cell membranes, which meant a high readiness of cells to implement apoptosis. However, there was found an inhibition of neutrophil death in time (compared with neutrophils, CD95-expressed in healthy people), which means the presence of immunity failure in patients with severe septic diseases due to the imbalance between pro-apoptotic and anti-apoptotic cytokines. Some circulating blood levels of cytokines and acute-phase proteins are known to be higher than normal in COPD patients. It has not yet been investigated how baseline therapy for COPD affects their dynamics. The objective of the study by Malo O., Sauleda J. et al[9,17,23] was to describe the changes occurring in the interaction system of some proinflammatory cytokines circulating in the blood during exacerbation of the disease in severe COPD patients and to assess the potential effect of ongoing corticosteroid therapy. The investigators measured serum TNF-alpha, IL-6 and IL-8 and CRP levels in 10 patients with severe COPD during the first 24 hours of hospitalization for suddenly increased respiratory failure, and repeated laboratory tests were done at discharge and 2 months later. A control group of 8 healthy subjects of the same age was recruited (24). According to the results, serum IL-6 levels were significantly higher in patients with COPD compared with the control group, and serum IL-8 levels in the control and COPD patients were similar. There was no statistically significant change in the studied indicators neither during the improvement in the course of the disease (despite corticosteroid therapy), nor after 2 months. Thus, the results demonstrated the presence of systemic inflammation during an exacerbation of COPD, which was virtually unchanged even under the influence of intravenous corticosteroid administration [23]. The determination of TNF-alpha by ELISA is of low sensitivity and is not recommended for this study. An interesting study was carried out by M. Miravitlles et al. [17] aimed to determine the role of elevated serum IL-6 or its

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soluble receptor (sRIl-6) levels in inflammatory system activation in patients with alpha1-antitrypsin deficiency. 7 people with alpha1-antitrypsin deficiency and 23 people diagnosed with COPD with the same degree of obstruction according to the EAP (SPH1 35.5-38.3%) were examined. Patients of both groups were comparable in age (51-63 years). By comparing serum IL-6 and its soluble receptor levels in the two groups, patients with alpha1-antitrypsin deficiency had average serum IL-6 and soluble IL-6 receptor levels of 4.7 pg/ml and 129.1 ng/ml respectively, while those with COPD with normal alpha1-antitrypsin levels of IL-6 and sRIl-6 were 4.1 pg/ml and sRIl-6 140.8 ng/ml respectively. And only one patient with alpha1-antitrypsin deficiency had higher than normal IL-6 levels. Thus, statistically insignificant differences in IL-6 levels and serum IL-6 receptor were found in both patient groups, meaning that there is no difference between the two. However, a dynamic study of these cytokines against the background of therapy has not been performed [7,9,21,25].

The alveolar macrophage is now considered to be the central cell of inflammation and the regulator of complex intercellular interactions. Lymphocytes, fibroblasts, monocytes, and T-lymphocytes become significantly activated as a result of alveolar macrophage activation. Activated T-lymphocytes secrete interleukin-2, under the influence of which effector T-lymphocytes are activated and produce a number of lymphokines. In addition, T-lymphocytes, as well as alveolar macrophages, produce several substances that stimulate fibroblast proliferation and hence the development of fibrosis.

Alveolar macrophages hyperproduce a range of bioactive substances, including interleukin-1, which stimulates T-lymphocytes and attracts them to the site of inflammation, i.e. the interstitial tissue of the lungs and alveoli [26].

The role of macrophages in immunity is extremely important: they ensure phagocytosis, processing and presentation of antigen to T-cells, secrete lysozyme, neutral proteases, acidic hydrolases, arginase, many components of complement, enzyme inhibitors (plasminogen antagonist, alpha2-macroglobulin), transport proteins (transferrin, fibronectin, transbalamin II), nucleosides and cytokines (TNF-alpha, IL-1, IL-8, IL-12). IL-1 has many important functions: by acting on the hypothalamus, it induces fever; it stimulates the release of neutrophils from the bone marrow; and it activates lymphocytes and neutrophils. Macrophages are one of the tools of innate immunity. In addition, macrophages, along with B- and T-lymphocytes, are also involved in the acquired immune response, being an "additional" type of immune response cell: macrophages are phagocytic cells whose function is to "ingest" immunogens and process them for presentation by T-lymphocytes in a form suitable for the immune response [27]. T-lymphocytes recognize an infected macrophage by exposing on its surface the microbial antigen in complex with the MNS class II glycoprotein, which in this case serves as a macrophage signal. As a result of recognition, T cells release lymphokines that stimulate intracellular destruction of the pathogen by the macrophage.

Thus, therapy aimed at correcting the monocytic-macrophage system is a priority in patients with an inflammatory nature of the disease, at all stages of the inflammatory process and regardless of its localisation, both in the bronchopulmonary system and elsewhere.

CONCLUSIONS:

Assessment of chronic obstructive pulmonary disease progression should be performed by comparing clinical parameters of a patient's condition with indexes of external respiratory function and with inflammatory biomarkers, both specific and non-specific, as disease progression in this group of patients is caused by specific features of bronchial wall remodeling processes [28]. It is important to study the dynamics of proinflammatory cytokine levels to assess the possibility of the effect of drug therapy on slowing the progression of the disease [5,19].

It is known that the insidiousness of COPD is its slow but steady progression. The pronounced clinical symptomatology appears only in the advanced stage of the disease (stage 2). In its early stages, COPD is latent, without persistent clinical symptoms.

Improving our understanding of the nature of the disease - the pathogenesis of COPD - is an essential tool in influencing the main approaches to COPD classification, treatment and prevention. COPD needs to be, and can be, treated. There are treatment interventions that can reduce symptoms, slow down the progression of the disease and improve patients' quality of life.

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