Role of macrophages and cytokines in the formation of inflammation and progression of chronic obstructive pulmonary disease

G'.T. Kurbanov
Samarkand State Medical University

Abstract: The article describes the role of macrophages and cytokines in the formation of inflammation and progression of chronic obstructive pulmonary disease.

Keywords: transforming growth factor TGF -β1, cytokine, inflammation

PURPOSE OF THE REVIEW

Consider some 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 observed in almost all countries of the world due to the constantly increasing prevalence and mortality from this disease. COPD is the only disease from which mortality continues to rise. According to a study by the World Health Organization and the World Bank, COPD will account for 5 percent of all deaths by 2020. COPD will become the 5th most common disease and the 3rd leading cause of death among all diseases.

It is known that acute or chronic alveolar-bronchial inflammation is a key factor in the pathogenesis of many pulmonary pathologies, such as bronchial asthma, COPD, adult respiratory distress syndrome and idiopathic pulmonary fibrosis. The localization and specificity of the inflammatory response may be different for each of these diseases, but all are characterized by the involvement and activation of inflammatory cells of the lung tissue. These activated cells can produce cytokines, oxidants, and many other mediators involved in inflammation [1–4]. The pathogenesis of COPD is based on chronic diffuse non-allergic inflammatory damage to the airways, in which neutrophils participate, with increased activity of myeloperoxidase, neutrophil elastases and metalloproteinases. The inflammatory response is associated with the infiltration of neutrophils at the site of inflammation with increased activity of interleukins -6 and -8, TGF -β1 and tumor necrosis factor-alpha (TNF-alpha) [5-7]. The inflammatory process is multifactorial in nature and represents a complex system of interaction between inflammatory cells, the cytokines and growth factors they

produce, as well as the activation of the receptor response of each group of cells involved in the inflammatory process. Increased sympathetic activity in patients with COPD promotes activation of the renin- angiotensin - aldosterone system (RAAS) and other neurohormones and mediators (cytokines, endothelin, vasopressin, etc.). It is now known that the inflammatory unit in COPD is small. bronchi, bronchioles and acini, where as a result of inflammation of the mucous and submucosal layers, thickening of the walls of the bronchioles occurs, hypertrophy of the smooth muscles of these structures and the involvement of the bronchiolar microenvironment in the inflammatory process, which potentiates the development of a vicious circle of inflammation, destruction of the interalveolar membrane develops [8-13]. The involvement of phagocytically 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 that regulate their production and interaction, as well as the recruitment of new immunocompetent cells to the site of inflammation, determines the degree of transition of reversible airway obstruction to irreversible and, therefore, determines the severity of COPD [7,14]. Neutrophils play a leading role in the pathogenesis of inflammation in COPD. Most proinflammatory cytokines are produced by neutrophils, activated lymphocytes, endothelial cells, and smooth muscle cells. Normally, proinflammatory cytokines should not be in circulation, but in some cases they can manifest themselves as a manifestation of latent inflammatory processes, as well as immunopathological conditions. Increased activity of the neurohumoral system stimulates the production of cytokines that have a pro-inflammatory effect, which determines the development of pathological changes. Cytokines are traditionally divided into interleukins (IL -1 - IL -15), transforming growth factor β1, tumor necrosis factors (TNF -alpha), [7,8,19,20]. TGF -β1 has a wide range of effects. Through TGF -β1-mediated induction of genes for growth factors, cytokines, transcription factors, receptors, mediators and acute-phase inflammatory proteins, as well as pyrogens, it is involved in the induction of cachexia. There is experimental evidence that activation of the cytokine system, mainly the production of TGF -β1, is associated with high activity of the SAS, RAAS and a state of chronic hypoxia [13]. As available data show, in the regulation of neutrophil apoptosis, the balance between pro-inflammatory and anti-inflammatory cytokines is important, ensuring timely removal of “excess” granulocytes after their function in the site of inflammation. However, when inhibiting neutrophil apoptosis, there is a risk of maintaining inflammation in the surrounding tissues, since neutrophils aggressively produce inflammatory cytokines, which is observed in patients with septic diseases when studying various markers of apoptosis in bronchoalveolar lavage, in biopsies of the bronchial mucosa and in the blood. Thus, activation of the cytokine system in

patients with COPD is a marker of disease progression with the involvement of more and more new components in the pathogenesis, including the human neurohumoral system, which leads to the appearance and progression of PH, which requires special pharmacotherapeutic tactics in the management of these patients [2, 6].

A study of neutrophils in patients with severe septic diseases revealed an interesting fact - the presence of a high percentage of neutrophils (compared to healthy people) with pronounced expression of CD 95 (ARO -1, Fas) on cell membranes, which meant a high readiness of cells for apoptosis. However, inhibition of neutrophil death over time was found (compared to neutrophils expressing CD 95 in healthy people), which means the presence of immune failure in patients with severe septic diseases due to an imbalance between pro-apoptotic and anti-apoptotic diseases. It is known that some levels of cytokines and acute phase proteins in the circulating blood in patients with COPD are higher than normal. It has not yet been studied how basic therapy for COPD affects its dynamics.

The researchers measured serum levels of TGF -β1, IL -6, and IL -8 in 35 patients with severe COPD during the first 24 hours of hospitalization for sudden onset respiratory failure, and repeated laboratory tests were performed at discharge and 2 months later. A control group of 30 age-matched healthy individuals was recruited (24). According to the results, serum levels of IL -6 and TGF -β1 were significantly higher in patients with COPD compared with controls, and serum levels of IL -8 were similar between control and COPD patients. No statistically significant changes in the studied parameters were observed either during the period of improvement in the course of the disease (despite corticosteroid therapy) or after 2 months. Thus, the results demonstrated the presence of systemic inflammation during exacerbation of COPD, which was practically unchanged even under the influence of intravenous corticosteroids [23]. An interesting study was conducted by M. Miravitlles et al. [17] sought to determine the role of elevated serum levels of IL -6 and TGF -β1 or its soluble receptor (sRIl -6) in activation of the inflammatory system in patients with alpha1 - antitrypsin deficiency. We examined 21 people with alpha1 - antitrypsin deficiency and 23 people diagnosed with COPD with the same degree of VAP obstruction (SPH 1 35.5-38.3%). Patients in both groups were comparable in age (51-63 years). Comparing the serum levels of IL - 6, TGF -β1 and its soluble receptor in the two groups, patients with alpha1 antitrypsin deficiency had mean serum levels of IL -6, TGF-β1 and soluble IL-6 receptor of 4.7 pg /ml and 129.1 ng /ml, respectively, whereas in patients with COPD with normal levels of alpha1 - antitrypsin 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 levels of IL -6 and TGF -β1 above normal. Thus, in both groups of patients, statistically non-significant differences were found in the levels of IL -6, TGF -β1 and serum IL -6 receptors, meaning that there is no difference between

them. However, a dynamic study of these cytokines during therapy has not been carried out [7,9,21,25]. The alveolar macrophage is currently considered a central inflammatory cell and a regulator of complex intercellular interactions. Lymphocytes, fibroblasts, monocytes and T lymphocytes are significantly activated as a result of activation of alveolar macrophages. 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 a number of substances that stimulate the proliferation of fibroblasts and, consequently, the development of fibrosis. Alveolar macrophages overproduce a number of bioactive substances, including interleukin -1, which stimulates T lymphocytes and attracts them to the site of inflammation, i.e., interstitial tissue of the lungs and alveoli [26]. The role of macrophages in immunity is extremely large: they provide phagocytosis, processing and presentation of antigen to T cells, secrete lysozyme, neutral proteases, acid hydrolases, arginase, many complement components, enzyme inhibitors (plasminogen antagonist, alpha2- macroglobulin), transport proteins (transferrin, fibronectin, transbalamin II), nucleosides and cytokines TGF -β1, (IL-1, IL-8, IL-12). IL-1 has many important functions: by acting on the hypothalamus, it causes fever; 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, also participate in the acquired immune response, being an “additional” type of immune response cell: macrophages are phagocytic cells whose function is to “absorb” immunogens and process them for the presentation of T -lymphocytes in a form suitable for the immune response [27]. T lymphocytes recognize an infected macrophage by displaying a microbial antigen on its surface 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, which stimulate intracellular destruction of the pathogen by the macrophage.

Thus, therapy aimed at correcting the monocyte -macrophage system is a priority in patients with the inflammatory nature of the disease, at all stages of the inflammatory process and regardless of its location, both in the bronchopulmonary system and in other organs.

CONCLUSIONS

Assessment of the progression of chronic obstructive pulmonary disease should be carried out by comparing clinical indicators of the patient’s condition with indicators of external respiratory function and inflammatory biomarkers, both specific and nonspecific, since the progression of the disease in this group of patients is due to the peculiarities of the remodeling process of the bronchial wall [28]. It is important to study the dynamics of the level of pro-inflammatory cytokines TGF -β1 (IL-1, IL-8,

IL-12) 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 lies in its slow but steady progression. Severe clinical symptoms appear only in the advanced stage of the disease (stage 2). In the early stages of COPD, it is latent, without persistent clinical symptoms. Improving our understanding of the nature of the disease - the pathogenesis of COPD - is an important tool for influencing the main approaches to the classification, treatment and prevention of COPD. COPD needs and can be treated. There are treatment interventions that can reduce symptoms, slow disease progression, and improve patients' quality of life.

References

1. Simbirtsev A.S. Cytokines are a new system for regulating the body's defense reactions. Cytokines and Inflammation 2002; 1(1)9-17.

2. Kantola I, Rauhala E, Erkinjunti M, et al. Sleep disturbances in hypertension: a double-blind study of isradipine and metoprolol. J. Cardiovasc Pharmacol 1991; 18:41-5.

3. Konishi M, Maito Y, Terao A. Trend in the development of coronary heart disease and its risk factors based on epidemiological studies. Jap Circulat J 1987; 51:319-24.

4. Levchuk Yu., Sobkovich -Vozniak V., Pishko P. et al. Atrial fibrillation in chronic obstructive pulmonary disease. Cardiol Pol 1993; 38(1)26-8. 5. Khodzhieva Dilbar Tadzhievna Safarov Komiljon Kamolovich. Study of neuropsychological symptoms and its clinical features in patients with covid -19. American Journal of Medicine and Health Sciences, 2021. 126–129.

6. Chung K.F. _ Cytokines in chronic obstructive pulmonary disease. Euro Respir J 2001; 18:50C-59C

7. Stephen M, Opal, MD, Vera A, De Palo, MD. Anti-inflammatory cytokines. CHEST 2000; 117:1162-72, 436 Varriale P, Ramaprasad S. Aminophylline induces atrial fibrillation. PACE - Pacing - Clin – Electrophysio. - 1993 October - R.1953 - 1955.

8. Nesterova I.V., Shvydchenko V. _ Regulation of apoptosis in the neutrophil-granulocyte system. Allergology and Immunology 2001; 2 (1):53-67

9. Tuev A.V., Mishlanov V.Yu. _ _ Clinical assessment of leukocyte function in patients with broncho-obstructive syndrome. Asthma - 2001; 2 (1):128-9

10. Freidlin I.S., Totolyan AA. Immunopathological mechanisms of inflammation of the bronchi and lungs. Mechanisms of inflammation of the bronchi and lungs and anti-inflammatory therapy. – St. Petersburg, 1998. – P. 194–298.

11. Khaitov V.A., Gusev E.Yu. _ Immunology of local and systemic inflammation. Allergology and Immunology 2001; 5:6–712. Adams D.H. _, Sham S.: Leukocyte -endothelial regulation of leukocyte migration. Lancet. 1994; 343:831-6.

13. Sharar S.R., Winn R.K. _, Harlan J.M.. Adhesion cascade and anti-adhesion therapy: A review. Springer Semin Immunopathol 1995; 16:359.

14. Demyanov A.V., Kotov A.Yu. _, Simbirtsev A.S. Diagnostic value of cytokine levels in clinical practice. Cytokines and Inflammation 2003; 2 (3): 20-35.

15. Samieva G. U., Olimjonova F. O. Acute purulent otitis media etiopatogenesis and clinical manifestation //Science and Education. – 2023. – Т. 4. – №. 2. – С. 462-468.

17. Samieva G. U. State of microbial landscape of upper respiratory tract in children with acute stenosing laryngotracheitis //European Medical, Health and Pharmaceutical Journal. – 2015. – Т. 8. – №. 1.

18. Malo O, Sauleda J, Busquets C, Miralles C, Noguera A. Systemic inflammation during exacerbation of chronic obstructive pulmonary disease. Thorax 2000; 55:114-20.

19. Muller R., Chanes P., Campbell A. _ M., Heusser K. Different patterns of cytokines in bronchial biopsies from asthma and chronic bronchitis. Respira Med - 1996; 90:79-85.

20. Kochetkova E.A., Volkova M.V. Cytokine status in patients with chronic obstructive pulmonary disease. 13 National Congress on Respiratory System Diseases 2003. - P.330.