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THE DEVELOPMENT OF ACUTE INFLAMMATORY CHANGES IN THE LUNGS AND THEIR TRANSITION TO PULMONARY FIBROSIS (LITERATURE REVIEW)

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ABSTRACT

Currently, acute and chronic lung diseases are the third most common cause of death, taking this place after cardiovascular and oncopathologies [1]. Despite the fact that acute inflammatory lung diseases, such as bacterial and viral pneumonia, successfully respond to etiotropic, pathogenetic and symptomatic therapy, in some cases severe and extensive damage to lung tissue occurs [2,3].

Acute lung injury (OPL) is a specific form of lung lesion characterized by extensive damage to the alveoli, non-cardiogenic pulmonary edema, as well as pulmonary and systemic neutrophil-associated inflammation, which leads to pulmonary insufficiency and hypoxemia [4-7]. Annually, OPL is diagnosed in more than 3 million patients worldwide, and mortality from this pathology varies from 35% to 46% [8,9]. Over the past few years, the incidence and mortality from OPL has increased significantly as a result of the pandemic of a new coronavirus infection caused by the SARS-CoV-2 virus (COVID-2019) [10,11].

Key words: fibrosis, inflammation, cardiovascular, pulmonary.

INTRODUCTION

Pulmonary fibrosis is a chronic, steadily progressive disease characterized by an overgrowth of connective tissue in the lungs and thickening of the alveolar septa, which leads to impaired respiratory functions, gas exchange and the development of pulmonary insufficiency [3,4]. Pulmonary fibrosis is a heterogeneous disease with a characteristic pattern of lung tissue damage, which

includes a large number of chronic diseases of the respiratory system accompanied by connective tissue growth in various lung compartments, such as interstitial lung disease (IBD) and idiopathic pulmonary fibrosis (ILF), which are the most severe representatives of this group of diseases due to irreversible and the progressive nature of fibrosis of the lung parenchyma [5-8]. The incidence of pulmonary fibrosis continues to increase both due to the development of diagnostic methods and due to the aging of the population. Currently, the incidence of ILF is 10 cases per 100,000 population, and IBD is 19.4 cases per 100,000 population [9,12]. The disease progresses at different rates in each individual patient, depending on age and gender [1], features of the lung microbiome [2], genetic and environmental factors In general, the 5-year survival rate ranges from 20 to 40% for patients with ILF [4] and from 55 to 75% for patients with IBD [5,6].

In most cases, the development of pulmonary fibrosis is preceded by acute pneumonia, which did not resolve on time and led to the deposition of connective tissue and impaired lung function [4]. Acute pneumonia can be caused by a variety of etiological factors, such as viral and bacterial infections, ionizing radiation, chemotherapy, irritants and air pollutants [7-10], It should be noted that the etiology of ILF is unknown, since no causal relationships or specific associations have been identified so far [1], but among the many internal and external risk factors, viral infections [13], gastroesophageal reflux disease (GERD) and associated micro-aspiration are given a separate place [2], as well as genetic predisposition [3,4]. GERD - one of the most significant risk factors for the development of ILF - is the most common disease among patients with ILF, affecting almost 87% of the total number of patients, however, the causal relationship between pulmonary fibrosis and GERD is still unclear and remains a topic for further research [5,6]. It should be noted that a number of authors emphasize the complexity of the processes occurring in the body of patients with ILF/IBD during the period of COVID-19 disease [7,8]. The usual clinical symptoms of pulmonary fibrosis are shortness of breath, unproductive cough, weight loss and chronic fatigue as a result of hypoxia [9].

In 2014, the FDA approved the use of pirfenidone and nantedanib for the treatment of pulmonary fibrosis [7]. Despite the importance of this event, since there were no approved antifibrotic drugs until 2014, the situation with pulmonary fibrosis therapy remains deplorable, since these drugs only allow to slow down the development of fibrosis, but not completely cure the patient. Moreover, some patients have severe adverse reactions to these drugs (gastrointestinal bleeding, severe diarrhea). As a last-line therapy, patients with pulmonary fibrosis undergo lung transplantation, which slightly increases their life expectancy. However, for

most patients, this treatment method is not possible due to the limited number of donor organs and the associated risk of transplant rejection. Therefore, the study of the molecular mechanisms of pulmonary fibrosis and the search for new molecular markers that can be used as targets for therapeutic agents that prevent the development of fibrosis seems extremely relevant. However, such a search is a difficult task, not least because of the complex pathogenesis of this disease.

In the presented review, the mechanisms and ways of transition of acute inflammatory changes of the lungs to pulmonary fibrosis will be considered, the pathogenesis of acute inflammatory processes in the lungs preceding fibrosis will be analyzed, the known molecular mechanisms of the development of pulmonary fibrosis are presented, the characteristics of the most common in vivo models and currently known prognostic markers of pulmonary fibrosis are given, and the latest discoveries in the field of standard and gene-directed therapy of the considered pathology.

The inflammatory component is a key factor in the development of pulmonary fibrosis, and its most frequent precursor is acute lung injury. Acute lung injury (OPL), as well as its consequence - acute respiratory distress syndrome (ARDS) - they are a specific form of lung inflammation, which is characterized by diffuse damage to the alveoli, non-cardiogenic pulmonary edema, as well as pulmonary and systemic inflammation, which ultimately leads to respiratory failure and hypoxemia [1-4]. Every year, more than 3 million people worldwide become ill with ARDS, and mortality from this pathology ranges from 35% to 46% [18,19]. The pandemic of a new coronavirus infection (COVID-19) caused by a coronavirus associated with severe acute respiratory distress syndrome (SARS-CoV-2) and named so because of the high homology with SARS-CoV-1, which caused an outbreak of severe respiratory distress syndrome in 2002-2003 [10,11,15]. Nevertheless, the etiological factors of OPL and ARDS in humans can be a large number of stimuli and diseases, such as bacterial (caused by Streptococcus pneumonia or Staphylococcus aureus [76,77]) and viral (caused by influenza virus or rhinovirus [8,9]) pneumonia, prolonged mechanical ventilation [8-12], exposure to chemicals (chlorine, phosgene and industrial substances [3-8]), the use of electronic cigarettes and vaping [6,7], acute brain injury [8,9], sepsis [1], acute pancreatitis [2] and many other pathologies.

The pathogenesis of OPL includes the development of a cascading inflammatory reaction in response to lung damage, which leads to an increase in the permeability of pulmonary capillaries and diffuse damage to the alveoli [93-95]. Alveolar macrophages are the first cells that come into contact with pathogens and irritants coming from outside, and also participate in the initiation and

resolution of the immune response in the lungs. In addition to these functions, alveolar macrophages perform non-immune, organ-specific functions, such as surfactant utilization, as well as absorption of apoptosing and destroyed cells [6-9]. In response to damage, lung macrophages switch to the pro-inflammatory (M1) phenotype and begin to secrete pro-inflammatory cytokines (TNF-a, IL-6, IL-1) and chemokines (IL-8, CCL7, CCL2), which leads to chemotaxis and progressive accumulation of monocytes and neutrophils in the alveolar space [2]. In turn, neutrophils release additional inflammatory mediators, reactive oxygen species and proteinases, which destroy the surfactant, basement membranes and the epithelial-endothelial barrier as a whole. Surfactant is a lipid-protein complex that is secreted by type II alveolocytes [100]. The functions of the surfactant are to reduce the surface tension of the alveoli, maintain them in a straightened form and prevent the appearance of pulmonary proteins in the lumen of the alveoli [11]. With the development of OPL, the death of type II alveolocytes leads to a sharp decrease in the secretion and degradation of surfactant and, as a result, the decline of the alveoli [12]. In addition, the pathogenesis of OPL and ARDS includes many factors such as imbalance of coagulation/fibrinolysis processes, apoptosis, and dysfunction of the antioxidant system [5]. The combination of these pathological processes leads to an increase in the dead, "unventilated" lung space, intra-pulmonary blood discharge and culminates in hypoxia, hypoxemia and pulmonary insufficiency [3].

Acute respiratory distress syndrome (ARDS) is a complex cascade process that often develops as a result of OPL and leads to fulminant respiratory failure and death [3, 12]. Currently, ARDS therapy is mainly symptomatic, aimed at relieving symptoms and often includes mechanical ventilation and the administration of corticosteroid hormones. However, the main efforts in the field of ARDS research are focused on the identification of prognostic biochemical and molecular markers that would make it possible to diagnose the progression of OPL and its transition to ARDS already in the early stages of the disease. In addition, timely diagnosis and prevention of the transition of OPL to ARDS plays an important role in preventing the chronization of the inflammatory process in the lungs and the development of pulmonary fibrosis, a chronic, steadily progressive disease accompanied by an overgrowth of connective tissue in the lungs [13].

Pathomorphologically, ARDS is represented by a pattern of diffuse alveolar lesions characterizing the exudative phase, which is accompanied by edema and the formation of hyaline membranes, and then passes into the proliferative phase with the development of reversible fibroplastic changes in the interalveolar septa and type II alveocyte hyperplasia [12]. A potential third and final phase of ARDS

may be pulmonary fibrosis. According to some data, the development of pulmonary fibrosis as an outcome of ARDS occurs in 4% of cases with an ARDS duration of less than one week; in 24% of cases, if the disease lasts from one to three weeks; and in 61% of cases, if the duration of ARDS is more than three weeks [14].

A cascade of inflammatory reactions in the acute phase of ARDS can lead to massive damage to the epithelium and endothelium in the lungs, followed by the release of anti-fibrinolytic factors, the launch of pathological regeneration, proliferation of smooth muscle cells and differentiation of fibroblasts into myofibroblasts, which eventually causes an imbalance between the synthesis and degradation of extracellular matrix components (ECM) and creates prerequisites for the development of fibrosis lungs [15]. One of the factors in the development of pulmonary fibrosis in ARDS associated with COVID-19 is a violation of immune mechanisms that occurs as one of the consequences of a cytokine storm [16] and causes damage to alveolar structures, as well as impaired functioning of matrix metalloproteinases and their inhibitors under the action of pro-inflammatory cytokines [17].

One of the most common chronic inflammatory pathologies of the lungs, accompanied by fibrotic changes, is bronchial asthma (BA), a heterogeneous disease, the main distinguishing features of which are persistent inflammation of the respiratory tract, as well as their hyperreactivity and reversible patency disorder [18,19]. Structural changes of the respiratory tract associated with the progression and chronization of asthma are combined under the broad term "remodeling of the respiratory tract" [20], which includes cellular and extracellular changes in the large and small airways: deposition of components of the VCM [12], violation of the barrier and transport function of the epithelium [13], goblet cell hyperplasia hypersecretion of mucus [14], proliferation of smooth muscle cells and fibroblasts/myofibroblasts [7], as well as intensive angiogenesis in the respiratory tract [4]. Chronic persistent eosinophilic inflammation in AD leads to the recruitment of lymphocytes and macrophages into lung tissue, which secrete pro-inflammatory mediators that stimulate the synthesis and secretion of chemoattractants for eosinophils by epithelial cells, fibroblasts and smooth muscle cells, thus closing a "vicious circle". In addition, according to some data, eosinophils themselves are profibrotic agents and play a role in the development of fibrosis in asthma [23]. Inadequate functioning of inflammatory-resolving signaling pathways leads to the fact that in the late stage of asthma, the inflammatory process passes from the respiratory tract to the lung parenchyma,

leading to chronic inflammation and irreversible changes not only in the respiratory tract, but also in lung tissue [4].

Thus, the most common outcome of acute inflammation is its timely resolution with subsequent restoration of damaged tissues. However, if it is impossible to eliminate the inflammatory factor, acute inflammation turns into chronic, and in some cases, persistent chronic inflammation can lead to the development of fibrosis. The development of fibrosis is based on an unregulated damage repair process (wound healing), and the main effector cells of this process are fibroblasts and myofibroblasts [15].

It has also been shown that one of the long-term effects of persistent pulmonary inflammation is hyperproliferation of lung cells, type 2 alveolocyte hyperplasia and squamous metaplasia of the bronchial epithelium, which are precancerous conditions [14].

Therefore, rapid and earlier prediction of severe course, possible complications and long-term consequences of OPL using specific biomarkers could improve the prognosis of patients with inflammatory lung diseases, which makes the search for such biomarkers an urgent task.

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