

The Role of Macrophage Endoplasmic Reticulum Stress System in Chronic Obstructive Pulmonary Disease Complicated with Pulmonary Hypertension

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Abstract: *Chronic obstructive pulmonary disease (COPD) is a respiratory disease with increasing morbidity and mortality. Pulmonary hypertension is a common complication of COPD. The endoplasmic reticulum protein folding balance plays an important role in maintaining cell function, and multiple stimuli can destroy the endoplasmic reticulum protein folding balance and induce endoplasmic reticulum stress. Endoplasmic reticulum stress is closely related to the occurrence and development of pulmonary hypertension. This paper mainly describes the changes of endoplasmic reticulum stress related biomarkers in COPD complicated with pulmonary hypertension, so as to provide a theoretical basis for the search of biomarker system for early diagnosis of COPD complicated with pulmonary hypertension, and facilitate the development of precision therapy drugs in the future.*

Keywords: *Chronic obstructive pulmonary disease; Pulmonary hypertension; Macrophage; ER stress*

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive and chronic inflammatory airway disease characterized by continuous airflow restriction, which seriously harms human health[1]Is a respiratory disease with increasing morbidity and mortality. A nationwide epidemiological study showed that the total prevalence of COPD in China in 2015 was about 13.6%, indicating that COPD has become a major public health problem[2]. COPD exacerbations will lead to higher mortality rates, and pulmonary arterial hypertension is a common complication of COPD exacerbations, patients with COPD combined pulmonary hypertension often leads to increased risk of sudden death, pulmonary hypertension seriously affect the daily life of the COPD patients, and patients with COPD exacerbations and death of one of the important reasons[3].Endoplasmic reticulum protein folding balance plays an important role in maintaining cell function. Various stimuli can disrupt endoplasmic reticulum protein folding balance and cause endoplasmic reticulum stress. Endoplasmic reticulum stress is closely related to the occurrence and development of pulmonary hypertension. Therefore, it is particularly important to study the pathogenesis of COPD complicated with pulmonary hypertension and to find a new diagnostic biomarker system so as to realize the early diagnosis. Previous studies have shown that macrophages play an important role in the pathogenesis of COPD and pulmonary hypertension, and endoplasmic reticulum stress plays an important role in macrophage inflammation. Therefore, endoplasmic reticulum stress system of macrophages has become a hot topic in the study of molecular mechanism of COPD complicated with pulmonary hypertension. This paper mainly describes the changes of endoplasmic reticulum stress-related biomarkers in COPD complicated with pulmonary hypertension, which is helpful to provide a theoretical basis for the search of biomarker system for early diagnosis of COPD complicated with pulmonary hypertension, and more conducive to the development of precision treatment drugs in the future.

2. Chronic obstructive pulmonary disease complicated with pulmonary hypertension is dangerous and has high mortality

Chronic obstructive pulmonary disease (COPD), as a chronic and recurrent disease, can involve adjacent pulmonary arterioles and cause vasculitis, thickening of the wall, stenosis or fibrosis of the lumen, or even complete occlusion, resulting in increased pulmonary vascular resistance and pulmonary hypertension. Pulmonary hypertension, as a progressive disease, seriously threatens the life of patients with poor prognosis[4]. COPD has become one of the top five causes of death in China in 2017, according

to the Global Burden of Disease Survey[5]. It is worth noting that COPD global initiative (GOLD) 2020 pointed out that over the next 40 years COPD prevalence will continue to increase, to 2060, there may be more than 5.4 million people die each year from COPD and its related diseases, prompt COPD combined pulmonary hypertension prevalence rate will continue to rise, increase the sick patients with COPD rate, mortality and burden on society[6]. Pulmonary hypertension is a chronic obstructive pulmonary disease at a certain stage of development, the key to combination of cor pulmonale, its progressive pulmonary vascular resistance increases as the main characteristics, which can lead to right cardiac insufficiency, and patients with pulmonary hypertension activity endurance, quality of life were significantly lower, and as there is no specific symptoms, often leads to delay in diagnosis, morbidity and mortality are very tall[7]. According to statistics, patients with COPD may have an average of 0.5 ~ 3.5 times of acute exacerbation and 0.09 ~ 2.40 times of hospitalization each year, and the fatality rate of hospitalization is as high as 10% ~ 60%[8]. The prevalence of pulmonary hypertension in COPD patients was 63%, with mild pulmonary hypertension accounting for 33% and moderate and severe pulmonary hypertension accounting for 15% respectively[9]. According to the report[10] The 5-year survival rate of patients with mild COPD combined with pulmonary hypertension was 50%, moderate to severe pulmonary hypertension was 30%, and extremely severe pulmonary hypertension was 0%. Clinical studies have shown that increased frequency and severity of COPD exacerbations are independently associated with all cardiovascular disease outcomes[11]. Acute exacerbation of COPD is the main cause of hospitalization, deterioration of lung function and death of patients with COPD.

3. Role of macrophages in COPD complicated with pulmonary hypertension

Macrophages are the key components of innate and acquired immunity of human body, and are the most important barrier to prevent the invasion of pathogenic microorganisms by producing effective host response. When the body is stimulated by cigarette smoke or pathogenic microorganisms, the cilia of respiratory mucosal cilia are shortened, the cilia swing ability is weakened, and the tight connection between cells is lost [12], which leads to the reduced phagocytic function of alveolar macrophages[13]. The phagocytosis of alveolar macrophages was significantly reduced in both COPD patients and healthy smokers[14]. And with the decrease of phagocytic ability of macrophages, the disease severity of COPD patients is higher, that is, the phagocytic ability of macrophages is positively correlated with the severity of the disease[15]. Therefore, most patients with COPD have abnormal function of alveolar macrophages, reduced phagocytic function of macrophages and long-term chronic inflammation in the airway, resulting in repeated aggravation of the disease, long-term hypoxia and subsequently pulmonary hypertension.

During the pathogenesis of COPD, alveolar macrophages are overactivated and can secrete a variety of inflammatory mediators, which can stimulate surrounding cells to participate in the regulation of chronic inflammatory response of COPD[16]. Alveolar macrophages form a complex cell network by activating and interacting with surrounding cells, and then participate in the development of COPD. Studies have shown that macrophages polarize into two distinct functional states, namely M1-type macrophages and M2-type macrophages, when participating in inflammatory responses[17]. Cytokines secreted by Th1 cells can induce the generation of M1-type macrophages, and M1-type macrophages can secrete a variety of cytokines, such as IL-12 and IL-6, which jointly participate in the Th1 immune response and ultimately lead to inflammatory injury[18]. Cytokines secreted by Th2 cells induce the formation of M2-type macrophages, which can secrete various cytokines such as TNF- α and IL-1 to participate in Th2 immune response, and jointly participate in tissue injury repair[19]. Although pulmonary hypertension was originally thought to be a vascular disease, there is a clear link between pulmonary hypertension and inflammation[20]. Evidence from basic and clinical studies indicates that inflammation can promote the formation of pulmonary hypertension and plays a crucial role in the occurrence and development of pulmonary hypertension[21]. A variety of inflammatory cells can promote the occurrence and development of pulmonary hypertension, among which mononuclear macrophages are more closely related to the occurrence and development of the disease[22,23]. Alveolar macrophages engulf foreign bodies, bacteria and other harmful substances in the airway, and under the action of macrophage chemotactic protein-1, they gather in the inflammatory area and produce respiratory outburst, producing and releasing superoxide anions and lysosomal enzymes, thus causing tissue damage[24].

The role of macrophages in pulmonary hypertension is two-fold. On the one hand, macrophages participate in specific and non-specific immune defense responses, and produce a variety of growth factors that regulate the proliferation and migration of interstitial cells and the synthesis of extracellular matrix proteins[25]. On the other hand, macrophages may up-regulate endothelin-1[26] And produce

reactive oxygen species and nitrogen vectors[27] And a variety of endogenous inflammatory factors such as IL-6, TNF- α and mononuclear factors mediate the production of pulmonary hypertension. It was found that the number of macrophages and mast cells in the pulmonary hypertension model group was significantly increased compared with the control group, and the number of macrophages could be significantly decreased after simvastatin intervention, and pulmonary hypertension was improved to a certain extent. Pulmonary hypertension in many forms[28, 29]In a macrophage model system, depletion or inactivation of macrophages may inhibit the development of pulmonary hypertension, including experimentally induced hypoxic pulmonary hypertension and portal pulmonary hypertension.

Macrophages play a key role in chronic airway inflammation in COPD complicated with pulmonary hypertension. Macrophages are "long-life" cells, which release cytokines, inflammatory mediators and chemokines after activation, chemotaxis and activation of CD8+ cells and neutrophils into the airway and participate in chronic airway inflammation. Currently on COPD combined pulmonary hypertension patients with alveolar macrophages research, its main macrophages from bronchoalveolar lavage fluid, induced sputum or surgical removal of the specimen, but bronchoalveolar lavage fluid, or the number of alveolar macrophages in induced sputum can not meet the demand of research, surgical removal of the source of alveolar macrophages in lung tissue specimen is enough, However, the number of patients with COPD complicated with pulmonary hypertension who can undergo lung tissue resection is limited and cannot meet the research needs, which restricts the research on the role of alveolar macrophages in the pathogenesis of COPD complicated with pulmonary hypertension.

4. Role of endoplasmic reticulum stress in COPD complicated with pulmonary hypertension

Endoplasmic reticulum is an important organelle for protein synthesis, folding and modification, lipid synthesis and calcium storage. When cells are subjected to adverse internal and external stimuli, unfolded or misfolded proteins can occur in the ER. These proteins do not have normal functional conformation, resulting in er dysfunction, called ER stress[30,31].Protein quality control has a complex system of monitoring, regulating er function, addressing ER stress and dysfunction, and this protective mechanism is called unfolded protein response (UPR). [32], is an adaptive cellular response that activates specific intracellular signaling pathways to protect er stress. UPR is characterized by three different downstream signaling pathways that promote cell survival or apoptosis, depending on the stressor, the intensity and duration of er stress, and cell type. UPR contains three classic pathways, namely inositolase 1 (IRE1) pathway, protein kinase R-like endoplasmic reticulum kinase (PERK) pathway and activated transcription factor 6 (ATF6) pathway. They control transcriptional and translational responses to the endoplasmic reticulum. In recent years, many studies have found that endoplasmic reticulum stress is closely related to the occurrence and development of pulmonary hypertension[33-36].There are many factors that induce the development of pulmonary hypertension such as hypoxia[34], virus infection[37], inflammation,[38]Endoplasmic reticulum stress can be induced.

ATF6 is an important molecule in endoplasmic reticulum stress. In the early stage of ER stress, ATF6 helps cells restore er homeostasis by activating and activating downstream signaling molecules, thereby promoting cell survival. ATF6 is then transferred to the Golgi apparatus and cleaved by S1P and S2P enzymes on the Golgi apparatus, in which the N-terminal (ATF6f) is translocated to the nucleus. Upregulation of molecular chaperone and er stress-related gene expression, enhanced protein folding and degradation capacity, increased protein transport capacity, and reduced er load [39,40].

When the stimulation is too strong or prolonged, the above responses are not enough to restore er homeostasis, and the cells activate the ER stress-related apoptotic pathways, promoting the injury of cell death. ER stress mainly activates enhancer binding protein homologous proteins (CHOP proteins), which induce apoptosis by inhibiting the expression of anti-apoptotic gene Bcl-2 or repair the mRNA translation process by forming heterodimer with ATF4, resulting in increased intracellular protein synthesis, ATP deficiency and cell death[41].

Several studies have confirmed that whether the lung tissue of patients with COPD, pure smoking rat COPD model joint cigarettes or lipopolysaccharide exposure the lung tissue of rat COPD model, or cigarette smoke disposal of AEC and bronchial epithelial cells, increased expression of endoplasmic reticulum stress, CHOP, the structure of the lung cell apoptosis increases 3 kind of phenomenon, and between change trend[42-48].The expression of ATF6, CHOP and inflammatory factors (IL-6, chemokine Ccl-2 and myeloid chemokine McP-1) increased in pulmonary arterial hypertension rats induced by monocrotaline[49]The expression of inflammatory factors IL-6, IL-1B and IL-2 was increased in pulmonary artery smooth muscle cells treated with endoplasmic reticulum stress inducer

lamycin, while treatment with endoplasmic reticulum stress inhibitor Salubrinal decreased the release of inflammatory factors[50]. Therefore, endoplasmic reticulum stress and subsequent inflammatory cascade may play a significant role in the pathogenesis of COPD with pulmonary hypertension, but the specific mechanism remains unclear.

5. Conclusion and Prospect

The study of disease biomarkers has important guiding significance for the development of new drug targets. At present, new biomarkers related to different mechanisms of pulmonary hypertension focus on many aspects, including endothelial cell function, inflammation, epigenetics, cardiac function, oxidative stress and extracellular matrix. Studies on biomarker systems such as ER stress and inflammation may provide effective basis for early clinical diagnosis, disease typing and severity judgment, and thus provide ideas for precise treatment of the disease and new drug development.

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