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Endoplasmic Reticulum Stress in the Diagnosis and Treatment of Diseases

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Abstract. Endoplasmic reticulum (ER) stress is a protective stress response of cells that takes place when the ER has a significant amount of unfolded and misfolded proteins. Endoplasmic reticulum stress that is prolonged and severe and the unfolded protein response it produces start the apoptotic cascade. Apoptosis brought on by endoplasmic reticulum stress has been demonstrated to be a crucial entry point for the detection and treatment of illnesses. Both Alzheimer's disease and pulmonary fibrosis are difficult to treat, and both are linked to aberrant apoptosis. As a result, one of the crucial research areas is the involvement of endoplasmic reticulum stress in the treatment of pulmonary fibrosis and Alzheimer's disease. At present, COVID-19 pneumonia is prevalent in the world and has become one of the main causes of pulmonary fibrosis. At the same time, recent studies have shown that people who are positive for COVID-19 are more likely to suffer from Alzheimer's disease. Therefore, the diagnosis and treatment of these two diseases are particularly important today. The purpose of this paper is to explore the triggering mechanism and physiological characterization of ER stress, and the prospects for the treatment and diagnosis of pulmonary interstitial fibrosis and Alzheimer's syndrome, which are still difficult to overcome.

Keywords: endoplasmic reticulum stress, unfolded protein response, apoptosis pathway, pulmonary interstitial fibrosis, Alzheimer's syndrome

1. Introduction

Endoplasmic reticulum (ER) is an important organelle for synthesis in cells, and it is an important participant in the production of proteins, esters and carbohydrates. About 30% of the proteins produced by cells are folded, modified and processed in the endoplasmic reticulum. Protein processing is disrupted when hypoxia occurs, nutrients such as glucose and amino acids are insufficient, and proteins secreted and produced in the endoplasmic reticulum are excessive, including gene mutations, which can lead to the accumulation of misfolded and unfolded proteins in the endoplasmic reticulum and trigger endoplasmic reticular stress. As shown in Figure 1, a large number of unfolded proteins bind to the BIP protein, dissociating the BIP protein from the PERK, IRE1α, and ATF6 proteins. The perk protein will autophosphorylate and phosphorylate the eIF2α protein to stop translation and shut down protein synthesis. At the same time, it promotes ATF4 to enter the nucleus as a transcription factor. IRE1α protein also undergoes autophosphorylation, then cleaves mRNA to synthesize new proteins, and enters the nucleus as a transcription factor, up-regulating the expression of some proteins such as chaperones. ATF6 enters the Golgi apparatus, cleaves to form the extremophore, enters the nucleus, and also acts as

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a transcription factor to upregulate protein expression. Prolonged and severe endoplasmic reticulum stress may lead to cell death.

This paper explores the prospect of endoplasmic reticulum stress in the treatment and diagnosis through literature research and review. The purpose of this study is to provide a direction and ideas for future research on the biotechnology of ER stress, and to provide a theoretical basis for the future treatment of this type of disease by the technology related to ER stress. At present, there are few studies on this, which mainly remain in describing the relationship between symptoms and cellular mechanisms. If the technology can be developed to treat pulmonary interstitial fibrosis and secondary hammer syndrome at the level of cellular mechanism, it will make a significant breakthrough contribution to the eradication of these two diseases, including the research of such diseases.

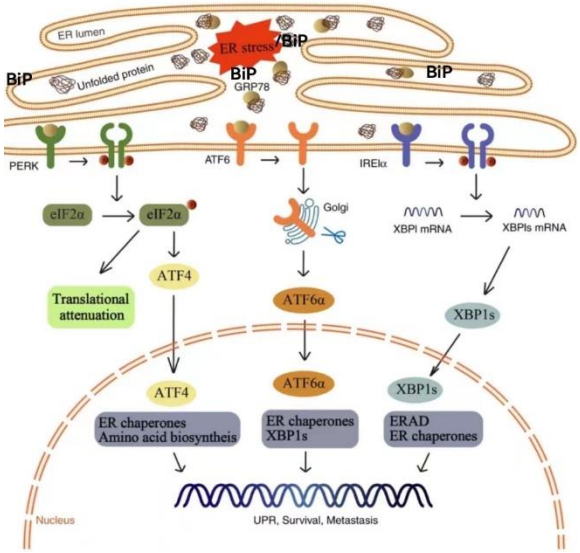

Figure 1. A variety of physiological conditions can disrupt the protein folding process and consequently result in the accumulation of unfolded and misfolded proteins in the ER stress [1].

2. ER stress in the diagnosis and treatment of pulmonary interstitial fibrosis

2.1. Introduction about pulmonary interstitial fibrosis

Interstitial pulmonary fibrosis is a terminal symptom of a large group of lung diseases. After the destruction of normal cell structure, abnormal repair leads to structural abnormalities, scar tissue formation, fibroblast proliferation and a large number of extracellular matrix aggregations, accompanied by inflammatory injury and tissue structure destruction, as seen in Figure 2. The initial symptoms were mainly dry cough and dyspnea, especially after exercise. In the middle and late stages, patients may suffer from dizziness, purple lips, toes, and other symptoms of hypoxia. For instance, pulmonary function may experience restrictive ventilatory dysfunction, abnormal blood analysis, hypoxemia, and respiratory alkalosis. If the condition deteriorates quickly, this can finally lead to respiratory failure and death [2]. Among them, the etiology of some patients with fibrosis is unknown. This group of diseases is called idiopathic interstitial lung disease, which is a major category of interstitial lung disease. Inhalation of dust, such as inorganic asbestos dust and coal dust, as well as organic dust such as mildew, is an important cause of pulmonary interstitial fibrosis in patients with clear etiology. Pulmonary interstitial fibrosis may also be caused by pathogen infection or the effects of drugs such as iodaminone. Among them, pneumonia caused by COVID-19, which is now raging around the world, has end-stage symptoms including pulmonary interstitial fibrosis. At present, there is no effective treatment for pulmonary interstitial fibrosis.

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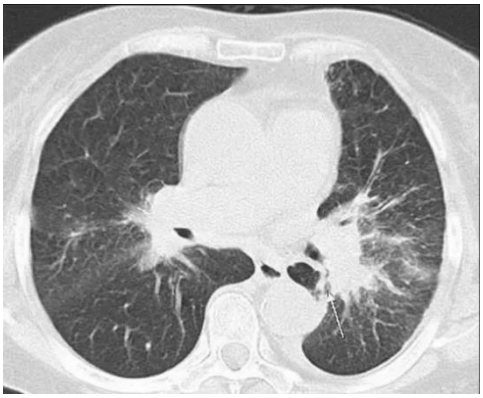

Figure 2. Pulmonary interstitial fibrosis in medical image (source from www.meipian.cn).

2.2. Potential treatment related to ER stress

There is an important link between epithelial cell apoptosis and fibrotic disease in the lung. Clinical studies have shown that the degree of ER stress is greatly improved in tissues with pulmonary interstitial fibrosis [3,4]. Prolonged pulmonary fibrosis leads to epithelial cell apoptosis through several unfolded protein reactions. The most important one is that ATF4 enters the nucleus and induces CHOP to activate IP3R, resulting in mitochondrial abnormalities and cytochrome C leakage, leading to apoptosis.

ER stress has an impact on cell differentiation in addition to apoptosis. For instance, XBP1 assists in plasma cell differentiation. When fibroblasts are activated and differentiate into myofibroblasts in fibrotic disorders, a lot of collagen and ECM are produced. Studies have revealed that after ER stress, fibroblasts are more prone to TGF—induced myofibroblast development. ER stress can cause EMT in epithelial cells. Although some studies have confirmed that EMT can not transform AEC into lung fibroblasts, the resulting cell phenotype can directly participate in fibrosis remodeling. In addition, cyclosporine can induce EMT in renal tubular epithelial cells by inducing ER stress [5].

Because the pathway of endoplasmic reticulum stress-induced pulmonary fibrosis is manifested in the signaling pathway and unfolded protein response, gene knockout of signaling pathway-related genes is an area of interest for many researchers. But doing so may also upset the balance of the system, and current experiments have shown that treatment with this method currently produces a strong cytotoxic effect rather than a therapeutic effect. Downstream effects of unfolded protein response, such as CHOP gene knockout, have been shown to have less impact on normal physiological homeostasis in vivo. Therefore, targeting the downstream effectors of ER stress may be an effective potential approach for the treatment of pulmonary fibrosis.

Another way to alleviate ER stress is to enhance the activity of chaperones through the effects of drugs. For example, 4-PBA and tauroursodeoxycholic acid (TUDCA) are beneficial in fibrotic model mice [6]. Of course, the relationship between the properties of these chaperones and cellular environmental homeostasis remains to be further explored, so the complexity and diversity of drug mechanisms and biochemical reactions must be taken into account.

3. ERS in the diagnosis and treatment of Alzheimer's syndrome

3.1. Introduction about Alzheimer's syndrome

Alzheimer's disease is a serious neurodegenerative disease, which is commonly seen in the elderly. In 2016, 40 million people had Alzheimer's disease worldwide, and 10 million of them are in China, with an average annual growth of 300,000 per year. It is expected that by 2050, the world will have 150 million patients with Alzheimer's disease, and China will have 30 million [7]. Its clinical manifestations are mainly memory decline, including severe near memory impairment and far memory impairment, which may be accompanied by mild depression symptoms in the early stage. In the middle and later stages, cognitive useability will also decline. The pathogenesis of Alzheimer's disease includes Aβ

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toxicity theory (senile plaque), abnormal TAU protein metabolism (NFTS), neuroinflammation theory, cardio-cerebral cascade theory, cholinergic deficiency and excitatory amino acid toxicity [8].

Extracellular amyloid beta protein deposition (also known as senile plaques) in the brain is the main pathological change of Alzheimer's disease. At present, the amyloid beta protein theory is the main theory of the cause of Alzheimer's syndrome. Current research seeks to control amyloid-beta production and fibrosis and deposition to prevent and treat Alzheimer's disease. However, this kind of treatment has no obvious effect. Current drugs can only delay the aggravation of symptoms, but they can not cure the disease, and they are easy to relapse after stopping the drug.

3.2. Potential treatment related to ER stress

One of the main symptoms of Alzheimer's syndrome is brain atrophy caused by apoptosis as shown in Figure 3. The apoptotic pathways of brain cell death include CHOP pathway, JNK pathway, caspase-12 pathway and GSK3/3β pathway. The abnormal apoptosis of cells will lead to the formation of holes in the brain, causing its symptoms.

The inhibition and attenuation of endoplasmic reticulum stress and its downstream responses are the main therapeutic research directions at present. Taurine (2-aminoethanesulfonic acid) is a free amino acid, which widely exists in the nerve center of mammals. Recently, Gharibani et al. Found that Taurine can inhibit and weaken the activation of endoplasmic reticulum caused by ischemia and hypoxia by blocking the activation of ATF6 and IRE1 pathways [9]. Parecoxib, a novel COX-2 inhibitor, can be used as a neuroprotective agent to rescue neuronal apoptosis mediated by endoplasmic reticulum stress after cerebral ischemia-reperfusion injury [5]. Ye Zhi et al. found that Parecoxib has a significant inhibitory effect on the expression of CHOP in the penumbra of blood loss, and can inhibit the immune activity of caspase-12, so as to slow down and control the apoptosis of nerve cells [10].

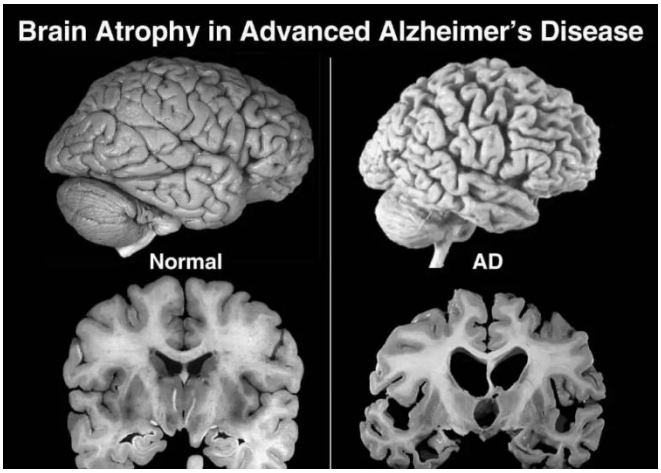

Figure 3. Brain Atrophy in Advanced Alzheimer's Disease (source from Chengdu Regional Cell Preparation Center).

Endoplasmic reticulum stress is very important and indispensable for the normal activity of cells and the protection of homeostasis in the body. But at the same time, abnormal apoptosis induced by ERS due to pathological reasons is also the pathogenic factor of many degenerative diseases. Among them, controlling the pathway of apoptosis can effectively alleviate the damage caused by degenerative diseases in the middle and late stages. Currently, unfolded protein responses can be controlled by knocking out genes involved in signaling pathways. It has been found that a small molecule inhibitor that can allosterically modulate the RNase activity of IRE1α oligomers can allow cells to survive ER stress, thus demonstrating that fine-tuning upstream UPR mediators may be beneficial [11]. At the same time, it is also one of the ways to treat degenerative diseases by enhancing the activity of chaperone proteins and accelerating the folding of unfolded proteins to avoid long-term endoplasmic reticulum stress.

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4. Conclusion

This paper investigates the role of ER stress in the diagnostic treatment of pulmonary interstitial fibrosis and Alzheimer's syndrome. The author analyzes the occurrence mechanism of ER stress, the effect of ER stress on apoptosis in lung interstitial fibrosis, and the treatment of lung interstitial fibrosis through ER stress related gene extraction and drugs to enhance the effect of partner protein activity. Besides, the relationship between apoptosis and Alzheimer's syndrome is also studied, as well as the alleviation of Alzheimer's syndrome by controlling ER stress through drugs. In conclusion, gene regulation and drug inhibition have relatively good effects on ER stress and its downstream unfolded protein response. It can be one of the main directions to the study of ER stress treatment

At present, only a few clinical experiments for this kind of research are carried out and there is no systematic theory and model for the effects of gene knockout and chaperone protein activity stimulation on the body's internal environment. In the future, with gene technology and protein regulation technology become more mature, the regulation of ER stress may becoming an important entry point and means for treating pulmonary interstitial fibrosis, Alzheimer's syndrome, and other similar diseases.

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