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The Mechanism of Ferroptosis in Asthma and Targeted Therapy: A New Perspective on Environmental Interaction and Clinical Translation

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Abstract: *Asthma is a common clinical respiratory disease with typical symptoms such as coughing, wheezing, chest tightness, shortness of breath, and dyspnea, which tend to worsen at night or in the early morning. Its pathogenesis is closely related to factors such as oxidative stress, immune imbalance, and abnormal cell regulation. In recent years, it has been found that ferroptosis is closely associated with asthma. This article explores the effects of environmental factors and genetic background on ferroptosis through the mechanism of ferroptosis in asthma, as well as therapeutic strategies targeting ferroptosis, providing a new perspective for clinical translational research on asthma.*

Keywords: *Asthma, Ferroptosis, Targeted Therapy*

1. Introduction

Bronchial asthma is a common respiratory disease characterized mainly by airway hyperresponsiveness and chronic airway inflammation. The essence and core of its onset are airway inflammation, and its pathophysiological feature is airway hyperresponsiveness. The incidence of asthma is also increasing year by year due to various factors such as air and environmental pollution, exposure to chemicals, and passive inhalation of harmful gases. The global incidence is about 1%-18% depending on the region, and the total number of asthma patients worldwide exceeds 339 million[1]. At present, bronchial asthma is mainly treated with glucocorticoids, but some people are insensitive to them, relapse after discontinuation, and long-term use has significant side effects on patients. Therefore, it is even more important to find new therapeutic targets, develop more effective treatment drugs and improve diagnosis and treatment guidelines. Ferroptosis is an iron-dependent and non-apoptotic form of programmed cell death that leads to an oxidative stress response when there is excessive accumulation of iron and lipid oxidation within the cells. During oxidative stress, reactive oxygen species (ROS), superoxide dismutase (SOD), and malondialdehyde (MDA) are involved. When asthma occurs, high concentrations of ROS can exacerbate apoptosis[2], thereby causing oxidative stress in lung tissue. Ferroptosis is associated with many respiratory diseases, but few have summarized the direction of asthma and ferroptosis. This article aims to discuss the association between ferroptosis and asthma, its possible mechanism of action, and potential ideas for targeted therapy.

2. The mechanism of the association between ferroptosis and respiratory diseases such as asthma

2.1 Iron homeostasis imbalance

Under physiological conditions, the absorption and metabolism of iron within cells maintain a dynamic balance. Ferroptosis depends on iron, and excessive iron accumulation triggers the Fenton reaction, through which iron produces ROS, and ROS catalyzes the formation of free radicals that drive lipid peroxidation, resulting in severe oxidative stress and cell membrane damage[3]. Philippot[4] et al. found iron deposition in macrophages in the lungs of chronic obstructive pulmonary disease (COPD), and the amount of iron deposition in the lungs increased with the severity of COPD and emphysema. Interleukin-6 is a pleiotropic cell that plays a central role in immune and inflammatory responses.

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According to the study by Han Fei[5] et al., IL-6 acts on bronchial epithelial cells, inducing ROS-dependent lipid peroxidation and disrupting iron homeostasis to promote ferroptosis in bronchial epithelial cells BEAS-2B. The regulation of lung iron levels also has an impact on the severity of asthma. In the clinical observations conducted by Khadem Ali[6] and in the mouse animal model of asthma induced by house dust mites (HDM), we found that compared with the control group, In patients with severe asthma, the number of iron-positive cells and the expression of iron uptake and storage molecules in the supernatant of bronchoalveolar lavage fluid (BALF) increased; In the HDM-induced asthma model, a significant increase in lung iron levels was observed. Similarly, a high-iron diet can cause iron accumulation, leading to an increase in lung iron levels. Additionally, it can induce many key characteristics of asthma, such as airway inflammation, high airway response, and airway fibrosis. These studies suggest that elevated iron levels play a key role in diseases such as asthma, and the regulation of iron levels is closely related to the disease mechanism and severity. Therefore, therapies that regulate iron levels in the lungs, correct systemic or local iron levels, and maintain iron homeostasis may have some therapeutic effect on the disease.

2.2 Oxidative stress and lipid peroxidation networks

Asthma, as a chronic airway inflammatory disease, forms a key regulatory network of oxidative stress and lipid peroxidation in its pathological process. The abnormal accumulation of reactive oxygen species in the airway microenvironment is one of the core characteristics of asthma. Excessive lipid peroxidation can induce ferroptosis, and ferroptosis can induce the production of reactive oxygen species, which accumulate and cause oxidative stress, thereby altering nucleic acids, proteins, etc., leading to cell damage and dysfunction[7]. Acyl-coa synthase Long chain family member 4 (ACSL4) and lysophosphatidyl acyltransferase-3 (LPCAT3) play an indispensable role in the biosynthesis and remodeling of polyunsaturated fatty acids (PUFA) in cell membranes and are key enzymes that promote lipid peroxidation in ferroptosis. Lipid peroxidation by-products such as 4-hydroxynonenal (4-HNE) and other harmful substances can further exacerbate cell damage. Glutathione peroxidase 4 (GPX4), a key regulator of ferroptosis, uses glutathione (GSH) to reduce peroxidized lipids to their corresponding alcohols, thereby inhibiting lipid peroxidation. Ferroptosis inhibitor protein 1 (FSP1), another important inhibitor of ferroptosis, works in conjunction with GPX4 to protect cells from ferroptosis [8]. Solute carrier family 7 member 11 (SLC7A11) is a key subunit of the cystine/glutamate reverse transporter (system Xc^-) that plays a significant role in regulating cellular ferroptosis. When intracellular oxidative stress intensifies, SLC7A11 function is impaired, GSH synthesis is reduced, GPX4 activity is decreased, and lipid peroxidation is out of control, ultimately leading to ferroptosis. In the study conducted by Song et[9] al., it was found that IL-17A and ferroptosis are important in asthma. IL-17A is an important regulator of ferroptosis in airway epithelial cells, promoting ferroptosis in airway inflammation in asthma. Inhibiting IL-17A can suppress inflammation and oxidative stress, thereby improving asthma and protecting cells from ferroptosis. IL-17A disrupts iron homeostasis and regulates lipid peroxidation-induced ferroptosis in asthma in ovalbuin-induced asthma model mice, and IL- 17A inhibition by the xCT-GSH-GPX4 antioxidant system protects airway epithelial cells from ferroptosis. The latest research shows[10] that CEACAM5, as a glycoprotein, can induce ROS accumulation, oxidative stress injury, lipid peroxidation and ferroptosis in lung tissue and human bronchial epithelial cells of asthmaic mice, while inducing ferroptosis and autophagy in bronchial epithelial cells by regulating the JAK/STAT6 pathway. This may open up new therapeutic approaches for clinical targeted asthma treatment.

3. Environment and Genetics

3.1 Environmental pollutants induce asthma and cause ferroptosis

In recent years, with the development of technology, environmental pollution has followed. For example, PM2.5, a toxic airborne particulate matter with a diameter of less than 2.5 μm, comes from natural pollution (forest fires, sandstorms, etc.) and anthropogenic emission pollution (vehicle exhaust, smoke dust, etc.). It has a strong irritant effect on human health, especially the respiratory tract. Epidemiological studies show that asthma attacks are positively correlated[11] with exposure to PM2.5 in the air. PM2.5 is an organic component with REDOX activity that induces oxidative stress, disrupts the airway mucosal barrier, and activates type 2 inflammatory responses that induce asthma[12]. CC16 is a 16 kDa protein secreted by respiratory epithelial cells and plays a significant role in host defense mechanisms. In the study conducted by Wang[13] et al., it was found that CC16 reduces airway inflammation induced by PM2.5 in asthmatic mice, possibly by inhibiting ferroptosis of epithelial cells

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through an antioxidant pathway. Cigarette smoke is a complex chemical mixture containing harmful substances such as carbon monoxide, nitric oxide, tar, which directly contaminate the air. Even in a well-ventilated environment, the harmful substances remain suspended in the air for a long time. The smoke exhaled by smokers and the smoke from burning cigarettes form second-hand smoke, which not only pollutes the air but also passively inhales the surrounding people. It irritates the mucous membranes of the respiratory tract, causing symptoms such as choking, wheezing and breathing difficulties. Tao et[14] al. observed airway hyperresponsiveness in mouse models of cigarette smoke (CS) exposure asthma worsening. IL-35 plays the role of an anti- inflammatory factor in preventing asthma, and NETs, as part of neutrophils, act as a bridge connecting innate immunity and adaptive immunity. In the CS exposure asthma model, NET release was increased and ferroptosis indicators were significantly elevated. IL-35 prevented the exacerbation of asthma in mice by inhibiting NET formation and improved CS exposure asthma by directly inhibiting NET formation through the STAT3/ ferroptosis axis. Coke oven emissions can cause a certain degree of air and water pollution and have a certain impact on human health. According to Chen Xian's [15] research, coke oven emissions can enhance allergen-induced lung inflammation and airway remodeling, and can work with house dust mites to cause ferroptosis in airway epithelial cells, possibly exacerbating asthma in the process. This provides an important clue for new asthma treatments targeting ferroptosis.

3.2 Genetic susceptibility and epigenetic regulation

Ferroptosis, as a novel form of programmed cell death, is closely associated with the occurrence and development of various diseases, among which asthma, as a common chronic airway inflammatory disease, has a complex pathogenesis involving genetic factors and epigenetic regulation. In recent years, it has been found that gene polymorphisms and epigenetic modifications play a significant role in asthma susceptibility and ferroptosis. Wang et[16] al. investigated the epigenetic regulatory mechanisms of H2B monoubiquitination (H2Bub1) and p53 in ferroptosis. The study found that H2Bub1 levels were reduced under the action of the ferroptosis inducer erastin, and the absence of H2Bub1 increased the cells' sensitivity to ferroptosis. H2Bub1 activates the expression of SLC7A11 through epigenetics. In addition, p53 is independent of its transcription factor activity, reducing H2Bub1 levels by promoting nuclear translocation of the deubiquitinating enzyme USP7 and inhibiting SLC7A11 expression when treated with erastin. The study revealed the link between p53 and ferroptosis through an epigenetic pathway mediated by H2Bub1, proposed the non-classical role of p53 in chromatin regulation, and provided a new perspective for understanding the regulatory mechanism of ferroptosis. The study by Shaheen et[17] al. examined the relationship between selenium status during pregnancy, glutathione peroxidase 4 genotype in offspring and childhood asthma. The study found that maternal blood selenium concentration was not significantly associated with the overall risk of childhood asthma or wheezing, but there was an interaction with the GPX4 genotype (rs713041). In children carrying homozygous T alleles at the rs713041 locus, for every doubling of maternal blood selenium concentration, the risk of asthma and wheezing decreased by 83% to 84%. Selenium status during pregnancy may regulate asthma susceptibility by influencing GPX4 activity and antioxidant defense, which in turn affects fetal airway epithelium. For specific susceptible populations (such as pregnant women with low blood selenium levels and children carrying specific GPX4 genotypes), selenium supplementation during pregnancy may help reduce the incidence of childhood asthma, but further validation through clinical trials is needed. GPX4 plays a key role in ferroptosis, a study that provides an important clue to the link between genetic susceptibility to asthma and ferroptosis. In the study of N6-adenosine methylation (m6A) and ferroptosis in children with allergic rhinitis - Asthma syndrome (CARAS) by Li et[18] al., it was found that m6A is a reversible RNA modification that affects gene expression through methyltransferase, demethylase and m6A recognition protein and is closely related to the immunomodulatory function of CARAS. Ferroptosis, as an iron-dependent mode of cell death, involves lipid peroxidation and is closely associated with the inflammatory response of CARAS. Studies have shown that m6A modification and ferroptosis play important roles in the occurrence, development and treatment of CARAS, for example, m6A affects ferroptosis by regulating GPX4 and thereby influencing CARAS progression. m6A and ferroptosis are expected to become new directions for the diagnosis and treatment of CARAS in children, and further exploration of their specific mechanisms in CARAS is needed to provide a new perspective for clinical diagnosis and treatment. Studies have found[19] that the epigenetic regulatory factor METTL3 plays a role in asthma and has an impact on ferroptosis. Overexpression of METTL3 can enhance the viability and proliferation of bronchial epithelial cells. METTL3 expression was significantly reduced in both OVA-induced mouse asthma models and IL-13-induced cell models. Mechanism studies have shown that METTL3 affects ferroptosis by modulating N6-methyladenosine (m6A) modification to regulate RNA stability of GPX4. Overexpression of METTL3 can suppress changes in IL-13-induced ferroptosis

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markers such as total iron, Fe2+, lipid reactive oxygen species, elevated malondialdehyde levels, and decreased glutathione levels, and alleviate asthma symptoms. The study reveals a new mechanism by which METTL3 regulates GPX4 expression through m6A modification, thereby influencing ferroptosis and the pathogenesis of asthma, providing a potential new target for asthma treatment.

4. New strategies for targeting ferroptosis in asthma treatment

4.1 The effects of ferroptosis inhibitors on asthma

Ferroptosis inhibitor protein 1 (FSP1) is located on the cytoplasmic membrane, and its N-terminal nutmeg acylation motif plays a key role in the process of anti-ferroptosis. As a NADPH-dependent CoQ (CoQ) REDOX enzyme, FSP1 inhibits ferroptosis by catalyzing the reduction of COQ[20]. Studies have found[21] that FSP1 inhibits lipid peroxidation by regenerating CoQ10 (CoQ10), and its reduced form (CoQ10-H2) can capture lipid peroxide free radicals, thereby preventing the spread of lipid peroxidation. The anti-ferroptosis function of FSP1 is not dependent on intracellular glutathione levels, GPX4 activity, ACSL4 expression or oxidizable fatty acid content, and is specific to ferroptosis inducers. According to the study by Sun Congconget al[22]., we found that intervention with the ferroptosis inhibitor Fer-1 alleviated histological changes in airway remodeling in asthmatic mice, and the expression level of GPX4 in the airway epithelia of asthmatic mice was upregulated, and collagen deposition around the airway and airway remodeling were alleviated, further confirming the role of ferroptosis in airway remodeling in asthma. Liproxstatin 1 (Lip-1), as an effective ferroptosis inhibitor, not only inhibits mitochondrial lipid peroxidation and reduces MDA levels, but also effectively regulates the expression[23] of GSH, GPX4 and ferroptosis inhibitor protein 1. Studies centered around ferroptosis inhibitors have shown that Liprox-1 significantly alleviates bronchial epithelial cell injury induced by lipopolysaccharide (LPS) and interleukin-13 (IL-13), and alleviates neutrophilic asthma by inhibiting ferroptosis. The mechanism may be that Lip-1 inhibits ferroptosis by up-regulating the expression of key ferroptosis regulators GPX4 and SLC7A11 and reducing ROS levels. Additionally, Lip-1 significantly reduces the expression of inflammatory factors and alleviates the inflammatory response. In mouse models, treatment with Lip-1 significantly improved neutrophil asthma induced by OVA and LPS, including lung tissue pathological changes, airway mucus secretion, inflammation, and ferroptosis. Small molecule inhibitors of ferroptosis such as these have the potential to open up new avenues for the treatment and intervention of asthma in future medical developments.

4.2 The efficacy of traditional Chinese medicine in treating asthma

With the continuous development and growth of traditional Chinese medicine culture, the holistic concept, syndrome differentiation and treatment, and other ideas in the exploration of asthma treatment have provided new ideas for precise intervention of asthma. Quercetin is a natural flavonoid compound commonly found in vegetables, fruits and traditional Chinese medicine. Recent studies have shown that in LPS/ OVA-induced neutrophil asthma mouse models, intraperitoneal injection of quercetin can reduce levels of inflammatory factors, alleviate the inflammatory response and airway collagen deposition in mice, and enhance cell viability and up-regulate the expression of antioxidant proteins SLC7A11 and GPX4 involved in ferroptosis to reduce ferroptosis [24]. Guben Fangxiao Yin, an empirical prescription of a professor of pediatrics in traditional Chinese medicine, has the effects of tonifying the lung and consolidating the exterior, strengthening the spleen and resolving phlegm. In the study conducted by Dai Xiaohan et[25] al., it was found to have a significant protective effect on the lung tissue of asthma remission model mice. It inhibits oxidative stress, lowers ROS levels in lung tissue, reduces inflammatory cell infiltration, lowers levels of inflammatory factors IL-4 and IL-5, improves mitochondrial function, enhances the activity of mitochondrial respiratory chain complexes, and increases ATP production. The mechanism of action may be related to the activation of the AMPK/Nrf2/HO-1 signaling pathway, which helps to enhance antioxidant capacity and reduce oxidative damage, thereby alleviating chronic airway inflammation. Hypericum, as an active ingredient in traditional Chinese medicine, is commonly found in plants of the Hypericum genus and has anti-inflammatory and antioxidant effects. Studies have confirmed[26] that it can alleviate airway inflammation and airway hyperresponsiveness by activating the Nrf2/HO-1 signaling pathway, reducing oxidative stress, lowering MDA levels, and increasing GSH and SOD levels. Anthocyanins [27], polydatin[28], amygdalin[29], etc. also improve the oxidative stress response to varying degrees by regulating this pathway, thereby alleviating asthma symptoms. Oxidative stress mediates ferroptosis, and antioxidant pathways have positive implications[30] for improving ferroptosis. A recent study also supported this view. Electroacupuncture, a therapy that combines traditional

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acupuncture with modern electrical stimulation techniques, improved lung function impairment, pathological manifestations of lung tissue, levels of inflammatory factors, and improved lung tissue ferroptosis [31] by down-regulating Keap1 and up-regulating Nrf2 expression in the asthma model group of mice. The development of traditional Chinese medicine culture has provided new insights for the clinical diagnosis and treatment of asthma, as well as some scientific basis for the clinical application of asthma.

4.3 Genetic intervention

In recent years, the prospects of gene editing technology, especially in the treatment of respiratory diseases, have attracted much attention. Some studies analyzed the GSE147878 dataset using methods such as WGCNA and found that CAMKK2 and CISD1 are key genes for ferroptosis associated with asthma. Their upregulated expression inhibits ferroptosis and may have an impact[32] on the immune microenvironment. Car-nk cell therapy uses gene editing techniques (such as CRISPR-Cas9) and CAR technology to precisely target and kill asthma- related cells, such as IgE secreting B cells and eosinophils. By editing the receptors of NK cells (such as NKG2A, KIR, etc.), their activity can be enhanced and asthma inflammation[33] reduced. Bioinformatics analysis revealed that ferroptosis-related gene AKR1C3 was significantly upregulated in the peripheral blood of asthma patients. In vitro experiments showed that overexpression of AKR1C3 reduced iron ion and lipid peroxidation levels in BEAS-2B cells and inhibited ferroptosis, while silencing AKR1C3 did the opposite[34]. Gene intervention techniques offer new hope for asthma treatment. By precisely regulating genes related to ferroptosis, it is expected to develop more effective asthma treatment strategies and improve patient prognosis, and further explore its potential for clinical application in the future.

5. Conclusion

The role of ferroptosis in asthma remains highly controversial. Although an increasing number of studies have revealed a potential link between ferroptosis and asthma, it remains unclear whether ferroptosis is a driver of asthma or a secondary phenomenon, suggesting the need for more longitudinal cohort studies to further verify the specific role of these genes in asthma. At present, most of the evidence supporting the association between ferroptosis and asthma comes from mouse models. However, human airway tissue is highly heterogeneous, which makes the transition from animal models to clinical applications challenging. Future research should focus more on the complexity of human airway tissue, using advanced technologies such as organoids or 3D airway models to enhance the translational value of research results. In addition, in-depth studies combining multi-omics analysis and clinical samples will help to gain a more comprehensive understanding of the mechanism of ferroptosis in asthma, thereby providing a more solid theoretical basis for the development of new therapeutic targets. Future research should focus on addressing the limitations of existing studies and exploring the exact role of ferroptosis in asthma, with the aim of providing more effective treatment options for asthma patients.

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