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Research Progress on the Regulation of Macrophages by Histone Modification in Bronchial Asthma

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Abstract: *Macrophages, a key component of the innate immune system, are closely associated with the occurrence and development of various lung diseases, such as chronic obstructive pulmonary disease (COPD), allergic asthma, acute lung injury, and idiopathic pulmonary fibrosis. Macrophages can differentiate into two types: the classical pro-inflammatory M1-like macrophages and the anti-inflammatory M2 macrophages. During the inflammatory process, these two types of macrophages are alternately activated. Therefore, it is extremely important to maintain the balance between the two types of macrophages. Epigenetics refers to the potentially heritable changes in gene expression without altering the DNA sequence. It is dynamic and reversible, including DNA methylation, histone modification, and non-coding RNA regulation. Among them, histone modification refers to the regulation of chemical modifications of histone tails, including methylation, acetylation, phosphorylation, ubiquitination, and lactic acidification, etc. An increasing amount of evidence indicates that the biological functions of macrophages are closely related to epigenetic modifications. Understanding the roles and mechanisms of macrophage-related epigenetic regulation can provide in-depth insights into the functions of macrophages in lung diseases. This article reviews the mechanisms of action of different histone modifications in macrophage polarization and their impacts on asthma, and describes the latest knowledge regarding the precise regulation of the biological functions of macrophages and their influence on asthma through epigenetic mechanisms.*

Keywords: *Histone Modification, Macrophage Polarization, Asthma, Epigenetic Regulation*

1. Introduction

Asthma is a respiratory disease with chronic airway inflammation as its core pathological feature, affecting approximately 300 million people globally [1]. Its typical clinical manifestations include wheezing, dyspnea, and chest tightness. It is characterized by airflow limitation, bronchial hyperresponsiveness, excessive mucus secretion, and airway inflammation, which lead to airway stenosis and cause symptoms such as wheezing, dyspnea, and chest tightness in patients. Recent studies have revealed that the pathogenesis of asthma involves a dysregulation of the interaction between the adaptive and innate immune systems. At the level of adaptive immunity, the disruption of the homeostasis of CD4+ T cell subsets is a key link, including two aspects: the imbalance of the Th1/Th2 ratio (when Th2 cells dominate, they secrete IL-4, IL-5, and IL-13 to promote eosinophil infiltration) and the imbalance of Th17/Treg functions (the pro-inflammatory cytokine IL-17 secreted by Th17 cells exacerbates neutrophilic inflammation), jointly creating a microenvironment in which inflammation persists [2].In the innate immune system, alveolar macrophages participate in the regulation of this process through M1/M2 phenotypic polarization: M1 macrophages secrete pro-inflammatory factors such as TNF-α to amplify the Th17 response, while M2 macrophages promote Th2 differentiation and airway smooth muscle proliferation through the secretion of TGF-β [3].Although the current mainstream treatment for asthma (inhaled glucocorticoids combined with long-acting β2 receptor agonists) can inhibit the Th2 pathway, it has poor efficacy for non-Th2 asthma (accounting for approximately 40% of clinical cases) and cannot reverse the formed basement membrane fibrosis. Moreover, the phenotypic polarization (M1/M2 balance) of innate immune cells, especially macrophages, has been found to have a two-way regulation with the adaptive immune response, which provides a theoretical basis for the development of novel targeted therapies [4].

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2. Macrophage

Macrophages are important immune phagocytic cells present in various tissues of the body. Most macrophages originate from bone marrow precursor cells that develop into monocytes. Macrophages have a high degree of heterogeneity. Monocytes derived from the bone marrow enter different tissues and organs of the body through the bloodstream and differentiate into various types of macrophages, which are named differently according to the tissues they are in. For example, microglia in the central nervous system, osteoclasts in the bones, Kupffer cells in the liver, alveolar macrophages in the lungs, etc. [5]. Macrophages can phagocytose foreign substances entering the body, such as pathogenic microorganisms and particulate matter, and can also eliminate waste in the body and recycle nutrients. Therefore, macrophages play an important role in maintaining tissue homeostasis and development in the body and regulating the inflammatory process. Lung macrophages include alveolar macrophages and interstitial macrophages, which originate from the same type of progenitor cells. Alveolar macrophages are located on the epithelial surface of the lung and are in direct contact with the environment. Compared with interstitial macrophages, alveolar macrophages are the main effector cells and participate in both pro-inflammatory and anti-inflammatory responses [6].

Macrophages can change their phenotypes and functions according to the changes in the local microenvironment, which is called macrophage polarization, including two types: classically activated M1 type and alternatively activated M2 type (Figure 1). Interferon (IFN-γ), lipopolysaccharide (LPS), tumor necrosis factor (TNF), etc. can induce macrophages to differentiate into the M1 type, secreting a variety of pro-inflammatory factors such as interleukin IL-6, TNF, IL-1β, IFN-β, IL-12, IL-23, and nitric oxide, exerting a pro-inflammatory effect [7]. Interleukins 4, 10, 13 (IL-4, IL-10, IL-13), etc. can induce macrophages to differentiate into the M2 type. M2 macrophages can be further differentiated into three subtypes: M2a, M2b, and M2c. M2a is produced by IL-4, IL-13, etc., M2b is produced by immunoglobulin complexes and TLR agonists, and M2c is produced by IL-10, TGF-β, etc. M2a can secrete IL-10, TGF-β, etc., leading to the occurrence of allergic inflammation. M2b can secrete TGF-α, IL-1, IL-6, IL-10, resulting in powerful anti-inflammatory and immunomodulatory properties. M2c can secrete TGF-β, IL-10, enabling anti-inflammatory tissues to exert a phagocytic effect. Different macrophages have specific biomarkers. Those of M1 are CD80, CD86, TLR-4, etc., and those of M2 are CD163, CD206, CD209, etc. [8]. By secreting different cytokines, macrophages play corresponding roles in different inflammations and diseases, which is beneficial to improving the body's inflammatory response and exerting anti-inflammatory and tissue repair effects [9]. The ratio of M1 and M2 macrophages is closely related to the function of the lungs, and the imbalance of M1/M2 determines the degree of inflammation in the body [10]. In response to the opposite effects of M1 and M2 macrophages, the body can regulate M1/M2 polarization and switch between anti-inflammatory and pro-inflammatory effects as needed to eliminate inflammation in the body.

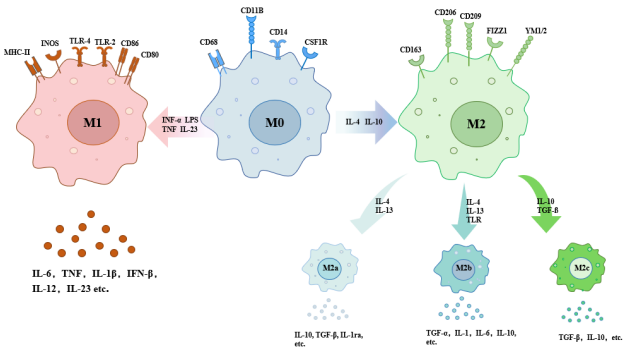

Figure.1 Schematic diagram of macrophage subtypes

Macrophages are an important component of the immune cells in the lungs and are involved in many respiratory diseases. As mentioned above, macrophages can be polarized into different types according to different signals in the microenvironment. When the body is exposed to allergens, the tissues undergo macrophage polarization to adapt to environmental changes [11]. In allergic reactions, M1 macrophages produce cytokines and chemokines, recruit T and B cells, and eliminate pathogenic microorganisms. M1 macrophages have a high expression level in non-allergic asthma. M2 macrophages are the main type involved in allergic asthma diseases, and an increase in the polarization and activation of M2 macrophages can be observed in asthma patients [12]. By changing the polarization of M2 macrophages, it can be used to treat or relieve allergic asthma. Nucleotide-binding oligomerization domain-like receptor

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protein 3 (NLRP3), autotoxin receptor (AMFR), and bone marrow-specific fatty acid-binding protein loss 5 (FABP5) have been shown to promote the polarization of M2-like macrophages, thus achieving the effect of relieving allergic asthma and providing therapeutic strategies for the prevention and treatment of allergic asthma [13].

Macrophage polarization affects the Th1/Th2 balance and plays an important role in the occurrence and development of asthma. Therefore, clarifying the mechanism of macrophage polarization in asthma is of great significance for the treatment of asthma [14].

3. Histone Modification

Epigenetics is a heritable regulatory mechanism that does not change the gene sequence. It is mainly determined by genetic factors but can also be influenced by environmental exposure factors. This process is variable and can undergo different changes under the influence of various factors such as different diseases, environments, aging, or others. Epigenetics is mainly divided into three categories: DNA methylation, histone modification, and non-coding RNA [15].

The nucleosome, as the basic unit of chromatin, is composed of DNA and a histone octamer [16]. The N-terminal tail structure of histones contains multiple amino acid residues (such as lysine, arginine, threonine, and tyrosine, etc.). Histone modification mainly occurs by affecting the free N-terminal tail structure of histones. Corresponding biochemical functional groups (such as acetyl groups, methyl groups, phosphate groups, lactate, etc.) can covalently bind to amino acid residues under the catalytic action of specific enzymes, thus generating post-translational histone modifications [17]. Histone modifications, including histone acetylation, methylation, lactylation, phosphorylation, etc., are extremely important in maintaining the stability of nucleosomes, changing the chromatin structure, and regulating gene transcription and inheritance [18]. Histone modification can affect various diseases by regulating macrophage polarization. For example, HDAC3, as a positive regulatory molecule of NF-κB-mediated inflammation, can inhibit IL-4-induced M2 polarization, and inhibiting HDAC3 is a potential therapeutic approach for preventing inflammation in chronic obstructive pulmonary disease (COPD). Similarly, mixed lineage leukemia 1 (MLL1), as a biomarker of inflammatory indicators and a key factor in activating macrophages, can drive the expression of TLR4 in diabetic macrophages and promote the polarization of M1 macrophages by mediating the methylation level of H3K4me3 on the TLR4 promoter [19], indicating that MLL1 is a target for treating refractory diabetic wounds.

Asthma is a major inflammatory disease. As a part of the immune system, macrophages play a dual role in inflammation, both promoting and inhibiting inflammation. By exploring the mechanism of macrophage polarization in asthma and combining the relationship between epigenetics and macrophage polarization, studying its internal mechanism can provide a potential help for the treatment of asthma.

4. Histone Modification of Macrophages in Asthma

4.1 Histone Acetylation of Macrophages in Asthma

Histone acetylation is a core mechanism of epigenetic regulation, and its dynamic balance is maintained by histone acetyltransferases (HATs) and histone deacetylases (HDACs) [20]. HDAC10 is one of the classes II HDACs. As a novel histone deacetylase, it plays a crucial role in cell cycle development, hormone regulation, lipid metabolism, and autophagy regulation. In asthma patients and animal models, it promotes M2 macrophage polarization by targeting the deacetylation of STAT3, which can significantly exacerbate allergic airway inflammation. It is worth noting that the loss of function of HDAC10 can inhibit the PI3K/Akt signaling pathway, thereby alleviating airway inflammation [21,22]. Based on this characteristic, unique asthma inhibitors may be developed. HDAC8, a member of class I HDACs, also cooperates with HDAC10 to regulate the phenotype of macrophages. Studies have shown that HDAC8 promotes M2 polarization by binding to the Galectin-3 protein, and inhibiting its activity can significantly reduce airway hyperresponsiveness (AHR) and inflammatory responses in an allergic asthma model. In addition to the HDAC family, the natural compound myricetin provides a new idea for the treatment of asthma airway remodeling by upregulating the expression of Sirt1 (a class III HDAC), reducing the phosphorylation and acetylation levels of JNK/Smad3, and doubly inhibiting macrophage inflammation and fibroblast activation [23]. At the level of positive regulation of acetylation, the role of the lysine acetyltransferase MOF (MYST1/KAT8) is particularly prominent. MOF is a lysine acetyltransferase (KAT) that not only regulates the cell cycle and autophagy by catalyzing the acetylation

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of histone H4K16 (H4K16ac), but also can perform acetylation modification at the K197 site of peroxiredoxin PRDX1 (PRDX1 K197ac) through targeting. This modification is rapidly downregulated in LPS-stimulated macrophages, and then promotes glycolysis and the release of pro-inflammatory mediators such as IL-6 by enhancing the phosphorylation of H3S28. It is worth noting that as a key factor in chronic inflammation, the production of IL-6 is dynamically regulated by the MOF-PRDX1 acetylation modification, which provides a precise target for blocking IL-6-related pathological processes (such as asthma airway inflammation) [24]. The above findings collectively reveal that histone-modifying enzymes form multi-level regulatory hubs in the pathogenesis of asthma by regulating the polarization of immune cells and the inflammatory signaling network. The development of drugs targeting these targets is reshaping the strategic system of asthma treatment.

4.2 Histone Methylation of Macrophages in Asthma

Histone methylation is catalyzed by histone methyltransferases and mainly targets the lysine and arginine residues of histones for site-specific modification. This process plays an important role in the regulation of macrophage polarization [25]. Studies have shown that the expression of M2 macrophage marker genes is dynamically regulated by H3K27 methylation: during the M2 polarization process, the expression of the H3K27 demethylase (Jmjd3) increases, leading to a decrease in the H3K27 methylation level [26]. Emodin regulates macrophage homeostasis through a dual mechanism - it can not only inhibit the removal of the H3K27me3 mark but also block the formation of H3K27 acetylation (H3K27ac) at the gene loci related to M1/M2 polarization, thereby weakening the excessive response of macrophages to polarization stimuli. This provides the possibility of restoring the balance of macrophages under pathological conditions [27]. In addition, α-aminobutyric acid (AABA) effectively inhibits M1 polarization by increasing the occupancy of trimethylation of H3K27 (H3K27me3) in the promoter region of M1 macrophage-related inflammatory genes, suggesting that it may regulate macrophage function through the interaction between metabolism and epigenetics and has potential for anti-inflammatory treatment [28]. Under inflammatory stimulation, LPS enhances the activity of Jmjd3 by activating the NF-κB signaling pathway, thereby reducing H3K27 methylation; while azithromycin (AZM) can inhibit this pathway and simultaneously down-regulate the methylation of H3K27me3 mediated by EZH2, controlling the progression of asthma by increasing the level of IL-10 in bronchoalveolar lavage fluid (BALF) [29]. It is worth noting that as a key demethylase, the selective inhibitor GSKJ4 of Jmjd3 can reduce the expression of CCL1 by blocking the binding of AhR to the CCL1 promoter, and Jmjd3-deficient mice also show a decrease in the expression of M2-related genes and the inhibition of the activity of pro-inflammatory macrophages (Figure 2). Since the expression of pro-inflammatory factors such as TNF-α and IL-6 is also regulated by histone methylation [30], targeting histone methylation modification genes related to macrophage polarization has become an important strategy for treating inflammatory diseases [26].

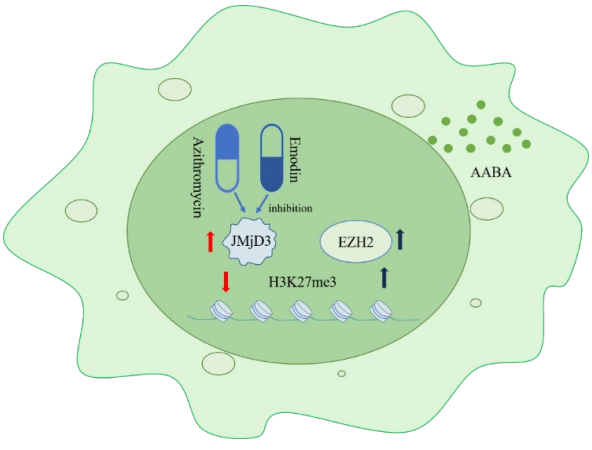

Figure.2 Schematic diagram of the influence of H3K27ME3 on DNA methylation

4.3 Histone Lactylation of Macrophages in Asthma

Lactate, as the end product of glycolysis, is not only a core mediator of energy metabolism but also a "multifaceted signaling molecule" that links immune regulation and epigenetics. In inflammatory diseases, lactate accumulation is common, and it is a key regulatory molecule for metabolism, immune responses, and intercellular communication [31]. Lactate accumulation affects the pathological process of

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diseases through a dual pathway: on the one hand, alveolar macrophages preferentially convert to glycolysis to rapidly supply energy during allergic airway inflammation, forming a barrier against inhaled allergens, which is considered a barrier against inhaled allergens in the pathogenesis of asthma [26,32]; on the other hand, lactate drives macrophage polarization by inducing histone lactylation. In 2019, a study found that histone lactylation increases in the late stage of M1 polarization of macrophages, promoting the conversion of M1 to M2 and transforming the pro-inflammatory response into an anti-inflammatory response, thus inhibiting inflammation [33]. In the resolution stage of inflammation, a fragmented mitochondrial network was found in macrophages. Compared with control macrophages, the inflammatory response to LPS was enhanced, and the signal transmission through the ATF4/c-Jun transcriptional axis was increased. Mechanistically, this occurs through the accumulation of lactate, leading to the lactylation of histones and a shift to an anti-inflammatory phenotype, demonstrating that mitochondrial fission promotes the inflammatory resolution response of macrophages through histone lactylation. This indicates that mitochondrial dynamics regulate epigenetic modifications in macrophages under inflammatory conditions [34]. Therefore, by targeting the glycolytic pathway and relating it to macrophages, potential therapeutic targets for asthma can be identified.

Metabolic processes include glycolysis, the pentose phosphate pathway, fatty acid metabolism, amino acid metabolism, one-carbon metabolism, and the tricarboxylic acid (TCA) cycle [35]. Recent studies have demonstrated that immune responses and metabolic processes interact with each other, and the metabolism of immune cells is also essential for inflammatory and anti-inflammatory responses. This deep interaction between metabolism and immunity is reshaping the treatment strategies for asthma: traditional corticosteroids (such as dexamethasone), although effective through immunomodulation, their effects are closely related to metabolism. For example, dexamethasone (DEX) can inhibit the HIF-1α glycolysis-lactate axis, reduce ovalbumin (OVA)-induced histone lactylation, and thus block anti-inflammatory signals [36–38].At the same time, studies have revealed that the immunometabolic network (glycolysis, TCA cycle, glutaminolysis) is closely related to macrophage polarization (Figure 3)— the activation of M1 macrophages depends on adenosine triphosphate (ATP) generated by aerobic glycolysis, which accelerates glutamine consumption, leading to the accumulation of TCA cycle intermediates (succinate and citrate) and amplifying inflammation. Blocking glycolysis with 2-deoxy-D-glucose and reducing the level of succinate can significantly reduce the inflammatory response of M1 macrophages[39-42]. The research team led by Chen further confirmed that targeting histone lactylation dependent on glycolysis can relieve eosinophilic asthma.

These studies collectively indicate that targeting lactate metabolism and its derived epigenetic modifications (such as histone lactylation) can achieve a two-pronged approach: it can not only cut off the pro-inflammatory energy supply of M1 macrophages but also reshape epigenetics to promote the resolution of inflammation, providing a new direction for the development of precision therapies for asthma.

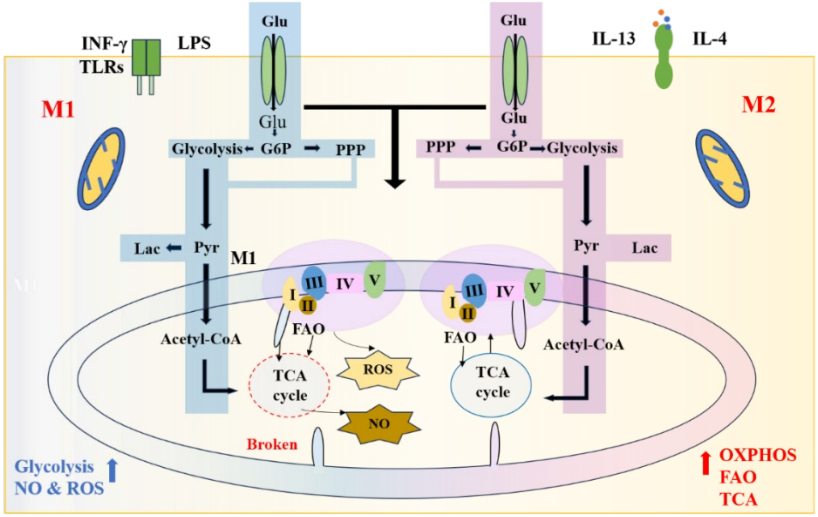

Figure.3 The relationship between the lactate cycle and macrophages

5. Conclusion

As a chronic inflammatory disease, the pathological process of asthma is closely related to

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macrophage polarization. As the core target cells for inflammation regulation, macrophages participate in the dynamic regulation of the balance between pro-inflammatory and anti-inflammatory responses through the M1/M2 phenotypic switch. This polarization process involves the cytokine network, chemokine gradients, transcription factor cascade reactions, and interactions between immunomodulatory cells. The complex regulatory network formed provides multi-level therapeutic targets for targeted intervention in asthma. Recent studies have shown that epigenetic regulation plays a crucial role in this process. Histone modifications (such as acetylation, methylation, and lactylation) precisely regulate the expression balance of pro-inflammatory genes and anti-inflammatory genes by dynamically changing chromatin accessibility[43]. Based on this mechanism, novel therapeutic strategies targeting epigenetic factors (such as HDAC, EZH2, and H3K27me3) have emerged. These breakthroughs not only open up a new path for the development of epigenetic drugs for asthma treatment but also deepen our understanding of the disease progression mechanism at the molecular level. Current research is advancing towards the direction of precision treatment. By integrating multi-omics technologies such as epigenomics and transcriptomics, and combining clinical translational research, individualized epigenetic regulation maps can be constructed. This strategy will promote the transformation of asthma treatment from a broad-spectrum anti-inflammatory mode to targeted epigenetic reprogramming. It can not only achieve molecular intervention in the early stage of the disease but also regulate the terminal pathological processes such as airway remodeling. With the progress of epigenetic biomarker identification technology, personalized epigenetic treatment regimens are expected to significantly improve the prognosis of patients and provide a new paradigm for optimizing the whole-course management of asthma.

Acknowledgments

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