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Research Progress and Treatment Strategy of Asthma

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Abstract

Asthma, as a common respiratory disease, is primarily caused by airway inflammation and airway wall remodeling, which are also its key pathological features. Its development is closely related to genetic, environmental, and immune system abnormalities. Asthma presents in a variety of phenotypes, including allergic, non-allergic, adult-onset, and persistent airflow limitation types, and these phenotypes may vary with age, gender, and environmental factors. In terms of treatment, inhaled corticosteroids, long-acting β 2 receptor agonists, and biologics have become standard therapeutic approaches. In recent years, biologics have provided new treatment hope for T2-high asthma, but further research is still needed for T2-low asthma treatment. Therefore, this review summarizes the epidemiological characteristics, pathophysiological mechanisms, disease classification criteria, and current treatment and prevention strategies of asthma, aiming to provide insights for future exploration of the disease's underlying mechanisms and innovative treatment methods, to alleviate the disease burden and improve patients' health outcomes.

Keywords

Asthma, Biopreparations, Targeted Therapy, Mechanisms of pathology

Asthma is a chronic respiratory disease characterised by airway inflammation and remodelling of the airway walls, presenting primarily with symptoms such as wheezing, shortness of breath, chest tightness, and coughing. As one of the most prevalent chronic respiratory conditions globally, asthma prevalence has been increasing annually across numerous countries [1, 2]. The development of asthma is closely associated with multiple factors, including genetic predisposition, environmental exposures (such as allergens and air pollution), and immune system abnormalities [3]. The aetiology of asthma is complex, with abnormal immune responses playing a pivotal role in its pathogenesis. Research indicates that allergic asthma is typically associated with excessive activation of Th2-type immune responses, where specific cytokines (such as IL-4, IL-5, IL-13) play a significant role in airway inflammation. Non-allergic asthma, conversely, may involve Th1-type or Th17-type immune responses. Abnormalities in these immune pathways are closely linked to the clinical manifestations, disease progression, and treatment response of asthma [4].

Asthma exhibits diverse phenotypes, with variations in patient symptoms, disease course, and pathological characteristics. Airway hyperresponsiveness leads to bronchoconstriction causing dyspnoea, a symptom often exacerbated at night or in the early morning. The core therapeutic objectives for asthma management are controlling airway inflammation, alleviating symptoms, and preventing acute exacerbations [5]. Inhaled corticosteroids form the cornerstone of asthma treatment, effectively reducing airway inflammation. Long-acting beta-2 agonists, leukotriene receptor antagonists, and anticholinergics are also commonly used adjunctive therapies [6]. Asthma management relies not only on pharmacological interventions but also on patient self-management. This paper comprehensively examines the epidemiological characteristics, phenotypic classification, pathological mechanisms, and therapeutic and preventive strategies

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for asthma, aiming to provide new perspectives and approaches for improving patient health outcomes and advancing the treatment of refractory asthma.

1. Epidemiology of Asthma

Although asthma is a non-communicable disease, it exhibits high morbidity and mortality rates [7]. Globally, asthma prevalence shows significant regional variation. Developed countries and regions such as North America and Europe demonstrate higher asthma prevalence, whereas in some developing nations—particularly low-income countries in Africa and Asia—there are often substantial gaps in asthma diagnosis and treatment. A survey of 3,875 asthma patients across 30 provinces, municipalities, and urban areas in China revealed that the asthma control rate in 2017 was merely 28.5%. According to household interview data from the Centre for Disease Control, the prevalence of asthma among Chinese adults rose to 8.7% in 2022, an increase from 8% in 2019 [8, 9]. Concurrently, numerous studies indicate that asthma incidence is particularly pronounced among children. The prevalence of asthma among children aged 6–11 years is 6.5% in the United Kingdom and 8.4% in the United States. The average annual prevalence of childhood asthma (9.5%) exceeds that of adults (7.7%). In China, the prevalence of childhood asthma increases by approximately 50% every decade, severely impacting children's health [10–12]. Furthermore, gender differences influence asthma. According to annual surveys by the US Centers for Disease Control and Prevention, asthma prevalence is higher among males than females during childhood, with males exhibiting rates approximately 30%-50% higher than females. However, upon reaching adolescence, the proportion of female asthma sufferers gradually increases. By adulthood, the proportion of female patients exceeds that of males by approximately 40%, with mortality rates among females being about 45% higher [13].

2. Phenotypic and Endotypic Classification of Asthma

As a significant inflammatory airway disease prevalent among both paediatric and adult populations, asthma represents a common chronic non-communicable condition. Its aetiology is complex and multifactorial, encompassing but not limited to respiratory infections, excessive physical exertion, climatic fluctuations, environmental pollutants (such as dust mites, mould, and pests), intense emotional fluctuations, specific medication use, and gastroesophageal reflux disease [14]. Diagnosis relies on a thorough understanding of its pathophysiological mechanisms and clinical manifestations, and asthma is now recognised as a syndrome comprising multiple endotypes and phenotypes. Endotypes are defined by molecular mechanisms and therapeutic responses, whereas phenotypes represent observable characteristics arising from the interaction between genotype and environment [15]. Presently, asthma phenotype classification is widely employed in stratified management strategies. Although these classifications do not directly reveal the fundamental aetiological mechanisms of the disease, they correlate closely with multiple clinical characteristics including age, gender, ethnicity, obesity, smoking, drug sensitivity, and mental health status [16].

According to the Global Initiative for Asthma (GINA) classification, asthma is generally categorised into five phenotypes: allergic asthma, non-allergic asthma, adult-onset asthma, persistent airflow limitation asthma, and obesity-associated asthma. Among these classifications, age-related factors are particularly pronounced. Connie L Yang et al. [17] found that children over one year of age constituted 28–41% of all paediatric asthma cases. Furthermore, children experiencing breathlessness or severe breathlessness during the pre-school years exhibited significantly different phenotypes compared to adult patients [18]. Furthermore, according to Hanna Hisinger-Mölkänen's survey report [19], females diagnosed with asthma during childhood are more prone to experiencing asthma symptoms than males.

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Phenotypic analysis of lung function also indicates that early lung impairment is closely associated with later chronic airflow limitation (such as chronic obstructive pulmonary disease), with this risk being particularly pronounced in children with severe persistent asthma [20, 21].

To more precisely define asthma's inflammatory subtypes, induced sputum analysis has gained widespread clinical application. With its detailed, comprehensive, and diverse testing methods, induced sputum technology is considered the gold standard for determining asthma airway inflammatory phenotypes [22]. Based on induced sputum analysis, asthma can be categorised into four subtypes: eosinophilic asthma (EA), neutrophilic asthma (NA), mixed granulocytic asthma (MGA), and paucinegranulocytic asthma (PGA) [23]. Based on airway eosinophil infiltration, asthma is further subdivided into two intrinsic subtypes: Th2-dominant asthma (T2-high asthma) and non-Th2-dominant asthma (T2-low asthma). T2-high asthma is primarily Th2 cell-mediated, commonly observed in EA and MGA, with its pathogenesis involving the overexpression of cytokines such as IL-4, IL-5, and IL-13. T2-low asthma, conversely, lacks prominent Th2 cell involvement and is predominantly mediated by Th1 and Th17 cells. It is frequently observed in NA and PGA, exhibiting more complex pathological features and demonstrating poorer responsiveness to anti-inflammatory treatments [24, 25].

3. Pathological Mechanisms of Asthma

3.1. Airway Inflammation

The airway inflammatory mechanisms in asthma patients are complex, broadly categorised into T2-type and non-T2-type asthma. In T2-type asthma, eosinophil infiltration is a defining feature [26]. Research indicates that type 2 innate lymphoid cells (ILC2) play a key regulatory role in T2 inflammation, with their numbers significantly increased in inflammatory diseases such as asthma, allergic rhinitis (AR), and sinusitis with polyps [27]. ILC2s accelerate disease progression by promoting Th2 cell secretion of cytokines such as IL-4, IL-5, and IL-13. Furthermore, ILC2s can induce naive CD4+ T cells to Th2 polarisation via IL-13 and may function as antigen-presenting cells [28].

Conversely, EA is characterised by elevated blood and airway eosinophil counts alongside heightened IgE reactivity, typically observed in allergy-related inflammation. Mixed-granulocyte asthma (MGA), however, involves both eosinophil and neutrophil participation, presenting a complex inflammatory pattern [14]. In contrast, non-T2 asthma exhibits more intricate pathophysiological features, dominated by Th1 and Th17 cells alongside neutrophil involvement and the release of various inflammatory cytokines (including IL-1β, IL-6, IL-8, IL-17, IFN-γ, and TNF-α) [29]. Non-T2 asthma typically presents with greater severity, marked airway remodelling, and reduced responsiveness to anti-inflammatory therapies. Further research is required in this field to elucidate its pathogenic mechanisms and therapeutic strategies.

3.2. Airway Remodelling

Asthma is a disease characterised by chronic airway inflammation, accompanied by airway hyperresponsiveness and airflow limitation. Typical symptoms include recurrent episodes of wheezing, breathlessness, chest tightness, and coughing [30]. Airway remodelling represents a crucial feature in the progression of asthma from a reversible condition to an irreversible pathological state, constituting a key step in disease advancement. Airway remodelling denotes structural and functional alterations in the airway wall arising from chronic inflammation and repeated repair processes following injury. These changes encompass recurrent damage to airway epithelial cells, thickening of the basement membrane, smooth muscle hyperplasia and

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hypertrophy, mucus gland hyperplasia, and angiogenesis. Collectively, these pathological changes lead to airway wall thickening, airflow limitation, and diminished elasticity.

Chronic inflammation serves as the core driver of airway remodelling. Inflammatory cells such as eosinophils, mast cells, and T lymphocytes induce abnormal proliferation of airway epithelial and stromal cells by releasing leukotrienes, cytokines (e.g., IL-4, IL-13), and other mediators, thereby stimulating excessive extracellular matrix deposition [31]. This process ultimately results in permanent alterations to the airway wall, markedly increasing airway narrowing, hyperresponsiveness, and airflow limitation, while simultaneously diminishing patients' responsiveness to pharmacological treatment. The irreversibility of airway remodelling presents a significant challenge in asthma management. In-depth investigation into the molecular mechanisms of airway remodelling holds considerable importance for improving patient symptoms and prognosis.

3.3. The Gut-Lung Axis

Although asthma pathogenesis is closely linked to immune responses and genetic factors, recent research has revealed a strong association between the gut microbiota and the onset and progression of asthma, termed the ‘gut-lung axis’. The ‘gut-lung axis’ denotes interactions between the gut microbiota and the lungs, exerting influence through pathways involving the immune, nervous, and endocrine systems. Both the gut and lungs maintain close connections with the immune system, with the gut immune system being recognised as the body's largest immune organ [32]. The gut microbiota influences systemic immune responses via the gut immune system, and these immune responses may in turn regulate pulmonary immune responses, thereby affecting the progression of diseases such as asthma. The gut microbiota exerts significant regulatory effects on the immune system, modulating systemic immune responses by influencing immune cell activity and cytokine secretion. Specifically, it plays a crucial role in balancing regulatory T cells (Treg) and effector T cells (Th2, Th17, etc.), which are central to immune responses in allergic diseases like asthma [33].

Recent studies have revealed that the composition of the gut microbiota in asthma patients differs from that in healthy individuals. Asthma patients typically exhibit reduced gut microbial diversity, an increased proportion of harmful bacteria in the gut, and a decrease in the abundance of probiotic bacteria (such as Bifidobacteria and Lactobacilli). This dysbiosis is thought to potentially promote the onset and progression of asthma. The gut microbiota interacts with the intestinal immune system to facilitate the establishment of immune tolerance. By producing metabolites such as short-chain fatty acids (SCFAs), gut microbiota can stimulate the generation of regulatory T cells (Tregs), which help maintain immune tolerance and reduce abnormal immune responses to foreign substances like allergens [34]. Dysbiosis of the gut microbiota may disrupt immune tolerance, increasing sensitivity to allergens and thereby triggering allergic diseases such as asthma.

This dysbiosis not only impacts the systemic immune system but may also directly influence airway immune responses via the gut-lung immune axis. Abnormal gut microbiota may alter intestinal epithelial barrier function, leading to the release of inflammatory mediators and cytokines. These substances enter the lungs via the bloodstream, activating airway immune responses and thereby contributing to the onset or exacerbation of asthma. During microbiota dysbiosis, impaired intestinal barrier function may increase intestinal permeability [35]. This barrier dysfunction permits undigested food particles, allergens, and harmful substances to enter the systemic circulation, triggering systemic immune responses and inflammation. Via the gut-lung immune axis, these inflammatory mediators can influence airway immune responses, exacerbate airway inflammation, and potentially promote asthma development. The gut microbiota influences the airway immune microenvironment by modifying the immune system's response to the airways. Under normal conditions, the gut microbiota helps regulate

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allergic responses through immune tolerance mechanisms, suppressing the development of airway allergic reactions. However, during dysbiosis, the airway immune system may become hyperactivated, leading to the release of inflammatory mediators and airway remodelling, thereby exacerbating asthma symptoms.

4. Treatment and Prevention of Asthma

Within the complex pathogenesis of asthma, various factors such as infections, allergies, and interactions with gut microbiota influence its onset and progression. As a complex clinical syndrome, asthma frequently presents with multiple complications [36]. However, precise modulation of the immune mechanisms in asthma patients, remodelling of phenotypes, and targeted drug intervention can effectively alleviate symptoms. The current asthma treatment approach advocated by GINA remains inhaled corticosteroids combined with short-acting and long-acting β2-adrenergic receptor agonists (SABA and LABA) [37]. For adult asthma patients, anti-inflammatory therapy constitutes the core strategy [38]. Mild asthma patients receive intervention only during episodes of breathlessness, typically involving fixed-dose combinations of inhaled corticosteroids (ICS) with formoterol or short-acting bronchodilators; For moderate asthma, maintenance therapy is recommended, comprising fixed-dose combinations of inhaled corticosteroids and long-acting beta-agonists supplemented with long-acting anticholinergics. Additionally, desensitisation therapy should be considered for some patients. In paediatric asthma management, most children present with mild to moderate disease. Good control is achievable through avoidance of triggers and/or pharmacological interventions including short-acting bronchodilators (SABAs), ICS, supplemented with long-acting bronchodilators (LABAs) and leukotriene receptor antagonists as required. Furthermore, biologic therapies have transformed severe asthma treatment, markedly reducing exacerbation frequency and diminishing ICS dependency. Currently available biologics for treating T2-dominant asthma target cytokines or cells within the T2 inflammatory pathway: omalizumab targets IgE, mepolizumab and relimuzumab target IL-5, benralizumab targets the IL-5 receptor, and dupilumab targets IL-4 and IL-13. For asthma presenting with different inflammatory patterns or co-occurring conditions, combination therapies with distinct biologics may be employed. Among these, the combination of omalizumab with anti-IL-5 agents represents the most frequently used therapeutic regimen for asthma [38].

In examining therapeutic advances for high-T2 versus low-T2 asthma, it becomes evident that while significant breakthroughs have been achieved in high-T2 asthma research, treatment pathways for low-T2 asthma remain uncertain. Consequently, identifying effective therapeutic strategies for this subset is particularly urgent and crucial. Eric Sze's investigation [29] indicates that non-pharmacological interventions (smoking cessation) can influence T2-low asthma management. Furthermore, dietary regulation has been found to affect asthma's pathophysiological processes: following a high-fat diet, genes mediating airway neutrophil recruitment show markedly increased expression, thereby exacerbating airway inflammation. Obesity resulting from prolonged high-fat diets may also indirectly exacerbate asthma symptoms by affecting respiratory mechanics. Consequently, smoking cessation, low-fat diets, and weight management for obese patients should be incorporated into comprehensive asthma treatment plans.

Addressing the limited response to ICS in T2-dominant asthma patients, studies indicate macrolide antibiotics may mitigate adverse effects associated with ICS. Macrolides are recognised for their anti-inflammatory properties and serve as primary antibacterial agents [39]. However, prolonged use may increase patient resistance and potentially cause adverse events such as gastrointestinal discomfort, hearing and balance disorders, microbial resistance, and cardiac effects [40]. Strict adherence to clinical indications and dosages is therefore

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essential. Moreover, long-acting muscarinic antagonists (LAMAs) represent an adjunct therapeutic strategy for asthma management. Incorporating LAMAs—particularly cetioramperidone—into conventional treatment regimens effectively mitigates asthma severity. Combining cetiorbrine with ICS significantly enhances patients' lung function. Although this effect is minimally related to the T2 inflammatory state, it markedly improves overall asthma management outcomes [41].

5. Summary

As a complex chronic respiratory disease, asthma is currently categorised into two primary subtypes: T2-high and T2-low. T2-high asthma is characterised by eosinophil dominance and is driven by Th2 cell-mediated immune responses, whereas T2-low asthma is neutrophil-dominant and exhibits poor responsiveness to anti-inflammatory therapies. Asthma management primarily relies on inhaled corticosteroids and β2-adrenergic receptor agonists. In recent years, biologics have offered new therapeutic prospects for severe asthma patients, particularly those targeting T2 inflammatory pathways such as omalizumab and relimuzumab, which effectively alleviate symptoms. Furthermore, asthma's pathophysiology is intrinsically linked to airway inflammation, airway remodelling, and gut-lung axis interactions. Airway remodelling represents a pivotal transition from reversible to irreversible airway disease, while gut microbiota dysbiosis is recognised as a significant contributor to asthma development and exacerbation. Investigating these mechanisms offers novel avenues for optimising therapeutic strategies.

In summary, asthma management continues to face multiple challenges, necessitating precise immune modulation, personalised treatment regimens, and the application of emerging biologics to enhance therapeutic outcomes. Future research should further investigate the pathological mechanisms of asthma and explore innovative targeted therapeutic strategies to reduce disease burden and improve patients' overall health status.

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