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Study the Immunology of Asthma: A Review of the Pathophysiology, Biomarkers, and Treatments of Asthma

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ABSTRACT: In addition to varying expiratory airflow limitation, asthma is a diverse disease characterized by a history of respiratory symptoms (such as wheezing, shortness of breath, chest tightness, and coughing) that change over time and in intensity. Later, the restriction of airflow could become permanent. A prevalent condition in both adults and children, asthma has a high global morbidity, death, and economic cost. Now that asthma is acknowledged as a diverse illness, new clinical and laboratory studies have clarified our knowledge of the immunology that underlies the condition. It is now recognized that asthma is a heterogeneous, complex condition with a range of hereditary and environmental components, where focused medicines lead to greater asthma control. Previously, asthma was thought to be a single diagnosis with standardized treatments for all individuals. Physicians may recognize asthma by endotype and develop more specialized and efficient treatment plans to better manage their patient's asthma by having a better understanding of the immunology of asthma. This comprehensive discussion of asthma immunology describes the causes and biomarkers now used in clinical practice, as well as the most advanced biological and specific treatments for asthma. From the review of this article, it can be concluded that articles were obtained with details of 18 articles containing information on Pathophysiology, Biomarkers, Immunology, and Treatments of Asthma.

KEYWORDS: Immunology; asthma; pathophysiology; inhaler; therapies.

1. INTRODUCTION

Asthma is one of the most common medical problems seen by primary care and specialist physicians, affecting more than an estimated 339 million people worldwide and associated with an enormous humanistic and economic cost. Approximately 300 million individuals worldwide have asthma, which is responsible for one out of every 250 fatalities worldwide. About 12 million Americans suffer from an acute asthma attack every year, with 25% of them needing to be admitted to the hospital. The severity of the disease may be incorrectly estimated by clinical assessments based on an interview and physical examination; for example, mild asthma is typically indicated by audible wheezing, while severe airflow obstruction may be indicated by no wheezing [1].

The aim of asthma management and treatment is controlling symptoms and minimizing increased risks. Therefore, it is crucial to remove the factors that cause airway inflammation and ultimately use medication to widen the constricted airway. Asthma is a complex causality, and each patient has a different clinical presentation. Neutrophils are primarily involved in the airway inflammation seen in specific asthmatic individuals. Airway remodeling brought on by chronic asthma includes goblet cell hyperplasia, smooth muscle hypertrophy, and subepithelial fibrosis beneath the basement membrane. This leads to intractable asthma, which is typified by persistent airway hyperresponsiveness and irreversible airflow limitation [2]

Asthma primary prevention although there are currently no proven methods for effectively preventing asthma in the first place, Global Initiative for Asthma (GINA) advises pregnant women and their unborn children to avoid environmental tobacco smoke, to have adequate vitamin D levels both before and during pregnancy, to give birth vaginally whenever feasible, and to avoid broad-spectrum antibiotics for the first year of life [3]. Advise that the optimum course of treatment for a given patient is the one that reduces symptoms, avoids flare-ups, and has minimal adverse effects. Additionally, it highlights that at every stage of care, comorbidity management, adherence and inhaler technique, and avoiding triggering variables (such as allergens) should be optimized [4]. The purpose of this review article is to provide a comprehensive

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overview of the current advancements in asthma therapy, examining the latest treatment options, emerging therapies, and the evolving understanding of asthma pathophysiology.

2. MATERIALS AND METHODS

This research is a review article. The review is written from original scientific articles or research related to pathophysiology, biomarkers, and treatments of asthma in the immunology of asthma. The original search for articles or research is sourced from search engines, namely Pubmed, Google Scholar, and Researchgate. Articles were obtained from the search after identifying the suitability with the inclusion criteria set; articles discussing studies on the pathophysiology, biomarkers, and therapies of asthma in the immunology of asthma are required for inclusion. A total of 37 articles were received, with details of 18 articles containing information on Pathophysiology, Biomarkers, Immunology, and Treatments of Asthma, with the most articles collected coming from searches on PubMed with several main keywords, such a Immunology; asthma; pathophysiology; inhaler; therapies. As a guide for producing this evaluation, the acquired journals were subsequently examined and evaluated, by evaluating article in the context of an article review, essentially offering a critical assessment of the article's strengths, weaknesses, and contributions to the field. A systematic approach will ensure that cover all key areas of the article while providing a balanced and constructive critique. The review essay describes the state of knowledge regarding a specific subject and offers a summary for further study.

3. RESULTS AND DISCUSSION

Immunopathophysiology of Asthma

Although the specific cause of asthma is unknown, risk factors have been found, and gene-environment interactions play a significant role. Given that the heritability of asthma ranges from 35% to 95%, genetics are known to play a part. Early-life respiratory infections, particularly those caused by viruses, raise the risk of developing asthma, especially if the symptoms are severe. Airborne environmental exposures, such as ozone, toxins, and tobacco smoke increase asthma risk. Asthma development is also linked to atopic disorders and sensitization to inhalant allergens [5]. Although a history of sinusitis, gastro-oesophageal reflux, or second-hand smoke exposure may indicate the primary cause of respiratory symptoms, these conditions are frequently also triggers for underlying asthma. A kid is more likely to experience chronic wheezing if they have a personal or close family history of an atopic condition, such as eczema, food allergies, or allergic rhinitis, particularly if symptoms start in the first year of life [6].

Both the innate and adaptive immune systems are activated in the immune pathophysiology of asthma in order to promote persistent airway inflammation. Airway remodeling, mucus clogging, mucus hypersecretion, and airway edema are the results of chronic airway inflammation. Subepithelial fibrosis, sub-basement membrane thickening, increased smooth muscle mass in the airways, angiogenesis, and mucous gland hyperplasia are the main causes of airway remodeling, which leads to long-lasting structural alterations [7]. Lower airway inflammation most likely results from a confluence of environmental exposures, genetic predisposition, and maybe modifications to the microbiota and metabolites (low molecular weight compounds in biological systems) [5]. The three primary roles of the epithelium lining the nasal and bronchial mucosa are mucociliary clearing of inhaled particles, innate immunological defense, and physical barrier function in preserving the respiratory mucosa's health. These systems work to stop inflammation and illness even when pollutants, allergens, or infectious agents are inhaled [8].

Immunology Response to Asthma

Due to significant advancements in our understanding of the possible processes behind the formation of asthma and its exacerbation, these pathways have been broadly classified according to the immunological components involved in its mechanism or therapy. Cytokines have a significant role in the onset and aggravation of asthma; research on how primary T_H2 cytokines affect human airway smooth muscle cells and explanted small bronchi smooth muscle cells indicates that IL-4 increased the potency of histamine, while IL-13 increased the potency of histamine, carbachol, and leukotriene D_4 as contractile agonists. As a result, the classical T_H2 cytokines IL-4 and IL-13 can alter how receptive airway cells are to mast cell products, thus revealing a mechanism by which enhanced responsiveness could result in asthma symptoms [9]. T_H2 cell

production is triggered by inhaled allergens presented by dendritic cells in the airway to naïve T-cells. Among the T_H2 cytokines released by T_H2 cells include IL-4, IL-5, IL-9, and IL13. IL-4, IL-9, and IL-13 stimulate B cells to release IgE. IgE then instigates mast cell degranulation and mediator release (histamine and leukotrienes), causing bronchoconstriction [7].

Allergic and eosinophilic asthma are two distinct classifications, both mechanistically driven by type 2 (T2) inflammation; high eosinophil levels are a common characteristic of both conditions. A variety of inflammatory cell types secrete interleukin (IL)-9, IL-13, and cysteinyl leukotrienes, which directly activate structural airway cells in both allergic and non-allergic eosinophilic diseases. These factors promote smooth muscle contraction, increased vascular permeability, immune cell recruitment, and mucus hypersecretion, all of which can result in fibrosis [10]

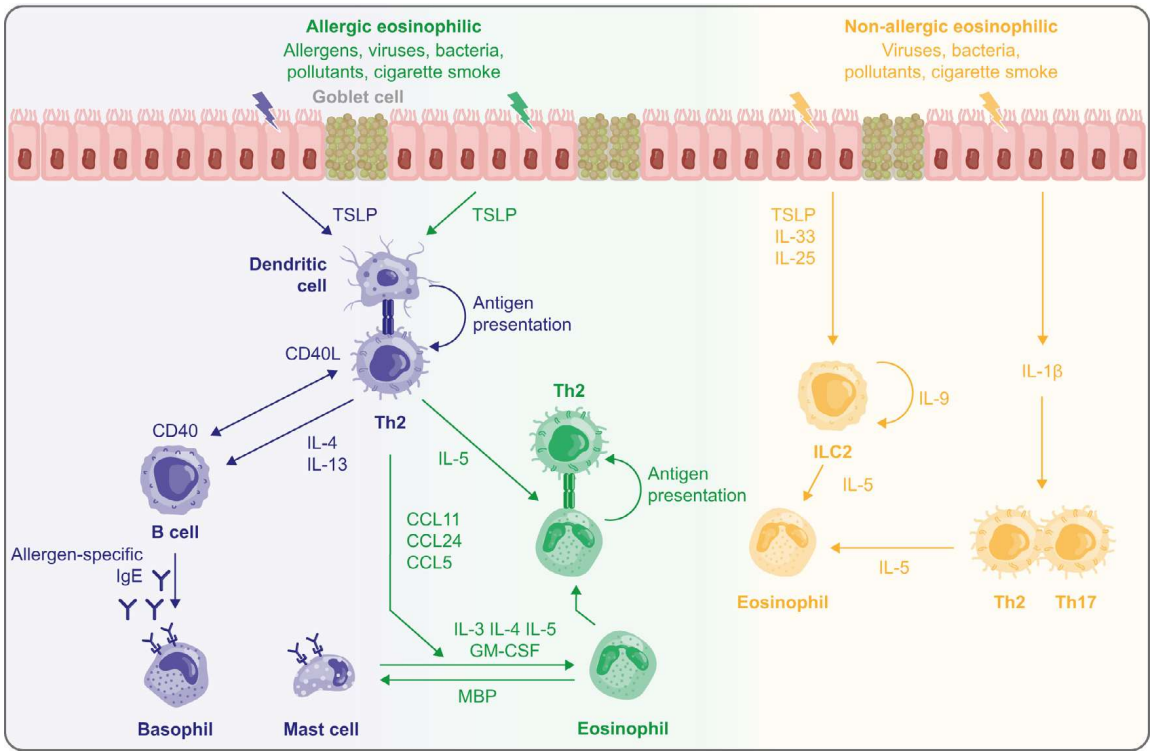

Figure 1. Underlying the inflammatory environment in both allergic and non-allergic eosinophilic asthma is immune cell signaling crosstalk. Mast cell and TH2 cell-secreted cytokines work together to enhance eosinophil recruitment to airway tissue in asthma with allergic and eosinophilic inflammatory characteristics. Stimulated innate lymphoid cells (ILC)2 in non-allergic eosinophilic release IL-5 and IL-13, which exacerbate the eosinophilic inflammatory environment but do not trigger IgE class switching, which is mainly triggered by IL4 [10].

Asthma Biomarkers

Traditional asthma biomarkers include eosinophils, neutrophils, IgE, periostin, fraction of exhaled nitric oxide (FeNO), and leukotrienes. Numerous potential biomarkers for asthma are being investigated, including volatile organic molecules, dipeptidyl peptidase-4, and cytokines [7]. Specialized leukocytes called eosinophils are primarily present in tissues, the respiratory system, and the mucosa of the airways. Eosinophils generate inflammation by producing a large number of inflammatory mediators, which, when combined with those released by T2 cells, result in bronchoconstriction, airway remodeling, and eosinophilic inflammation [11]. Early research measuring peripheral blood eosinophil counts discovered a signal of clinical improvement as the cells' numbers declined in response to treatment, as well as strong associations between the existence of these cells and the severity of the disease. Because it indicated the existence of the disease, its severity, and its response to treatment, the eosinophil was regarded as the definitive biomarker for asthma based on these associative findings, and it was thought to be the cell responsible for the condition [12]

Nitric oxide (NO) is synthesized by NO synthetases (NOSs).12 Patients with asthma have high levels of NO in their exhaled breath, which is thought to be due to upregulation of inducible NOS (NOS2) in airway epithelial cells secondary to airway inflammation [13] One method for identifying patients with corticosteroid-

responsive, T-helper cell 2 (Th2)-mediated airway inflammation is to measure the fraction of exhaled nitric oxide (FeNO), which can be done quickly and easily using chemiluminescence, electrochemical detection, or laser spectroscopy devices. FeNO assessment may offer a more practical and efficient method for identifying asthma and other corticosteroid-responsive inflammatory airway disorders when used in combination with symptom scores and lung function testing. Recent data indicates the upregulation of iNOS in the respiratory epithelium via STAT-6 and pro-inflammatory Th2-cytokines interleukin (IL)-4 and IL-13 [14].

Although dipeptidyl peptidase-4 (DPP-4) is expressed in several lung cells, it is unclear how it relates to asthma in humans. DPP-4 is present in bronchoalveolar lavage (BAL) in rat models and is associated with inflammation of the airways. There aren't many studies on DPP-4 in humans, but it's thought that IL-13 promotes its synthesis. Like periostin, DPP-4 can be detected in serum and could be used as a guide to induce anti-IL-13 therapy [11]. Specialized cells in the liver, kidney, spleen, pancreas, and lungs have membranes that express DPP-4. Adipocytes, endothelial cells, epithelial cells, and a variety of immune cells, such as macrophages, T cells, B cells, dendritic cells, and Invariant Natural Killer Cells (INKT) cells, all demonstrate high levels of its expression [15]. A biomarker is a property that may be tested and assessed objectively to serve as a predictor of pathogenic processes, normal biological processes, or pharmacologic reactions to a therapeutic intervention so that it can improve patient outcomes.

Treatments of Asthma

The goal of asthma treatment is to control symptoms and prevent future risks. Asthma treatment relies heavily on the long-term use of therapeutic medicines and the removal of asthma risk factors and triggers. Depending on the severity of the condition, asthma is treated with four stages of pharmacotherapy, each of which involves a daily dose of an inhaled corticosteroid that can range from low to high. The following characteristics are typically used to make a clinical diagnosis of asthma: (1) recurring symptoms, including coughing, chest tightness, wheezing, and paroxysmal dyspnoea; (2) reversible airflow restriction; (3) hyperresponsiveness of the airways; (4) inflammation of the airways; (5) an atopic condition; (6) exclusion of other cardiopulmonary disorders [2].

The Global Initiative for Asthma (GINA) no longer suggests using short-acting bronchodilators alone to treat asthma in adults and adolescents. To lower the likelihood of severe exacerbations, patients should instead be given a daily corticosteroid-containing inhaler or symptom-driven treatment (for moderate asthma). GINA conducted a thorough analysis of the data in 2019 regarding the adverse effects of SABA-only treatment, the influence of any ICS on asthma exacerbations and deaths in mild cases, and concluded that there was now enough data to suggest that SABA alone should not be used to treat adults and adolescents with asthma. The other "preferred controller option" for Step 2 is as-needed low-dose ICS-formoterol [16]. The combination of an inhaled corticosteroid (ICS) and formoterol, a particular long-acting bronchodilator, in a single inhaler for both maintenance and immediate relief treatment. One essential requirement for people with asthma is the prompt alleviation of their symptoms. Formoterol has the added benefit of a longer duration of action, although it still acts just as quickly as albuterol [17]

Updated National Asthma Education Prevention Program (NAEPP) guidelines were published in December 2020. These guidelines included recommendations for the use of ICSs intermittently and budesonide-formoterol as needed (also known as single maintenance and relief therapy). According to another study, adding formoterol to mometasone furoate maintenance medication decreased the incidence of asthma exacerbations. It did not raise the risk of significant asthma-related events [9]. Based on an overview of asthma medication in GINA 2024, when a low daily dose of ICS fails to achieve reasonable control of asthma, the addition of LABA to maintain ICS improves symptoms and lung function and reduces exacerbation. ICS-LABA is more effective than doubling the dose of ICS. Two regimens are available: (1) Maintenance-and-reliever therapy (MART), a combination of low-dose beclomethasone or budesonide with low-dose formoterol used for both maintenance and reliever treatment; (2) ICS-LABA as maintenance treatment plus SANA (or ICS-SABA) as a reliever. For adults and adolescents, MART is preferred [18]. A good therapy adheres to the most recent regulations in order to enhance patient outcomes.

4. CONCLUSION

Asthma is a chronic respiratory condition characterized by inflammation and narrowing of the airways, leading to recurrent episodes of wheezing, breathlessness, and coughing. The pathophysiology of asthma involves a complex interplay of genetic and environmental factors that trigger immune responses, particularly involving T-helper 2 (Th2) cells, eosinophils, mast cells, and IgE antibodies. These immune responses result in

airway inflammation, bronchoconstriction, and airway hyperresponsiveness. In asthma, inflammation leads to structural changes in the airways over time, such as airway remodeling, which contributes to long-term airflow obstruction. The triggers of asthma symptoms can vary and include allergens, respiratory infections, pollutants, cold air, and exercise. The goals of asthma therapy aim to achieve optimal management of the condition, improve the quality of life for individuals with asthma, and reduce the risk of asthma-related complications. These goals are typically achieved through a combination of pharmacologic treatment (e.g., inhaled corticosteroids, bronchodilators), non-pharmacologic measures (e.g., allergen avoidance, smoking cessation), and regular follow-up with healthcare providers.

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