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Understanding Asthma: The Role of Inflammation, Allergies, and the Immune System

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ABSTRACT

Asthma is a chronic inflammatory disorder of the airways marked by recurring symptoms such as wheezing, shortness of breath, coughing, and chest tightness. It is characterized by both allergic and autoimmune inflammatory responses that disrupt normal immune regulation. The interplay between environmental triggers and genetic susceptibility contributes significantly to the pathogenesis of asthma. Central to the disease mechanism are immune cells like eosinophils, mast cells, Th2 and Th17 lymphocytes, and a cascade of cytokines including IL-4, IL-5, IL-13, IL-17, and TNF-α. These cytokines facilitate airway inflammation, hyperresponsiveness, mucus hypersecretion, and structural remodeling. Regulatory cytokines like IL-10 and TGF-β attempt to restore balance but are often dysfunctional in asthmatics. A rising interest in the autoimmune component of asthma is evident, with autoantibodies and immune dysregulation being recognized in severe and steroid-resistant cases. Additionally, biomarkers such as FeNO and IgE levels are valuable in diagnosis and monitoring but are sometimes nonspecific. Allergic triggers like dust mites, pollen, and pet dander further complicate management, particularly in regions like Saudi Arabia, where allergic asthma is highly prevalent. Despite pharmacological advancements, heterogeneity in patient response necessitates personalized therapeutic strategies. A deeper understanding of immune pathways is essential for improving treatment outcomes. This review outlines the immunopathology of asthma with a focus on the cytokine network, allergic mechanisms, and immune dysregulation to provide insights for more precise and effective clinical interventions.

Keywords: Asthma, Inflammation, Allergies, Immune System

1. INTRODUCTION

Wheezing, shortness of breath, coughing, and chest tightness are all signs of asthma, a chronic inflammation of the airways. Although the precise origins of asthma are still unknown, it is known that environmental triggers and genetic predisposition both play a role in the disease's emergence [1]. Two processes that might be involved in the onset and development of asthma include allergic and autoimmune inflammatory responses. Wang et al. (2023) reported that elevated IgE levels are often seen in individuals with allergic asthma [2]. IgE plays a key role in allergic reactions by binding to allergenic substances and releasing chemicals that constrict the bronchial passageways and induce inflammation in the airways. The immune response against allergic responses and parasites involves eosinophils. Blood, sputum, or bronchial biopsies often show elevated eosinophil concentrations in asthma. Inflammatory chemicals released by eosinophils aid in the remodeling and inflammation of the airways. During inflammation, eosinophils and other cells in the airways create nitric oxide [3]. Fractional exhaled nitric oxide (FeNO) measurements may be used to measure airway inflammation, especially eosinophil inflammation, and track how well asthma patients are responding to therapy [4]. There are several drawbacks to using FeNO as a biomarker for airway inflammation in asthma, especially in relation to false positive findings. In addition to asthma, other illnesses may also cause elevated FeNO levels, which might result in false-positive test findings. For instance, even if they may not have asthma, people with eosinophilic bronchitis, allergic rhinitis, or even environmental factors like smoking or air pollution may have elevated FeNO levels [4,5,6]. (as shown in fig 1)

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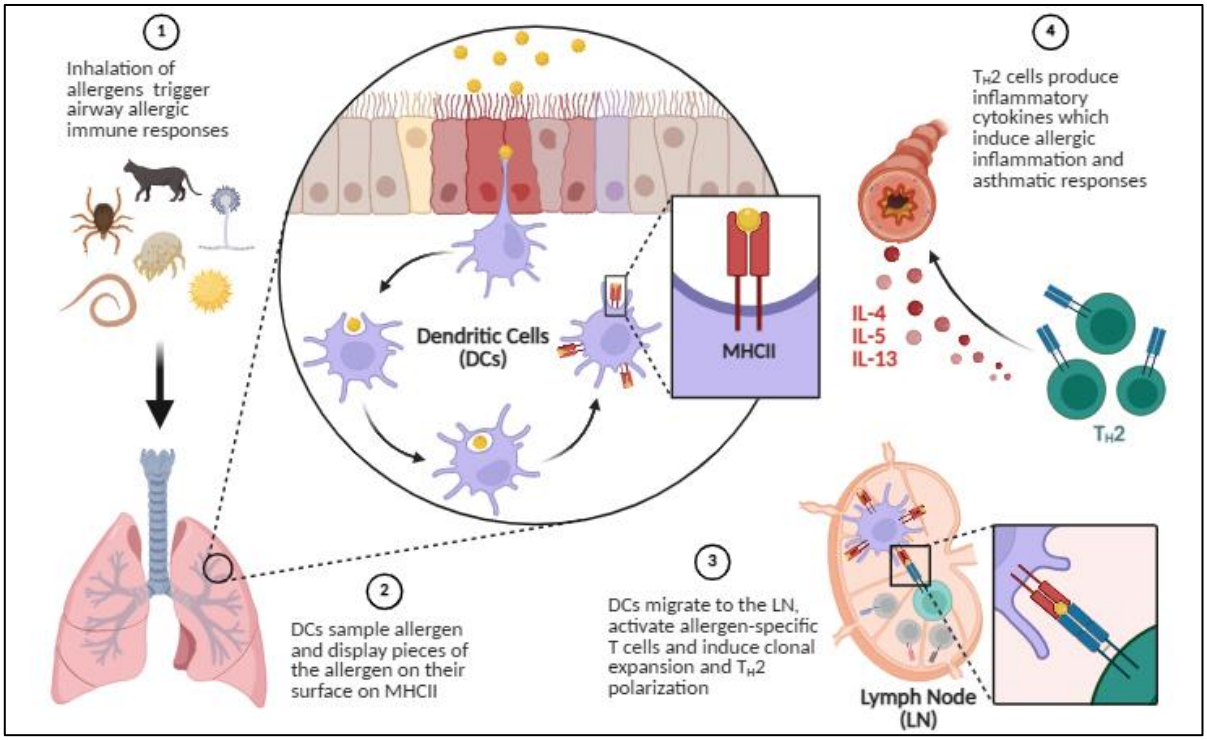

Fig 1: shows the trigger response pathophysiology of asthma.

An imbalance of immunological responses results from the immune system's dysregulation in asthma, which is a disruption of normal immune homeostasis. This dysregulation often shows up as an exaggerated immunological response, which includes enhanced airway hyperreactivity, overlap between allergy indicators, excessive synthesis of inflammatory cytokines, and hyperactivation of immune cells. But it may also result in an immune response that is insufficient or incorrect, which hinders the body's capacity to control inflammation and accelerates the course of chronic illness. The pathophysiology of asthma is based on this intricate interaction of immunological pathways [7]. Asthma is mostly a chronic inflammatory illness, but there is evidence that the condition may also develop and worsen as a result of dysregulated immune system pathways [8,9]. An immune system that is dysregulated in asthma may incorrectly target and assault respiratory system components. Autoantibodies that identify and attach to self-antigens in the respiratory system may be produced by some asthmatics [7]. They increase the disease's severity and chronicity, making it more difficult to treat with traditional asthma medications, by causing immune system dysregulation and encouraging ongoing inflammation [10].

T helper cells are essential for controlling immunological reactions. In asthma, there is evidence of a T helper cell imbalance, specifically a shift toward Th2 cell dominance [11]. Airway hyperreactivity and asthma symptoms are caused by the cytokines produced by Th2 cells, which encourage allergic inflammation. A particular subset of T cells known as regulatory T cells (Tregs) aids in preserving the equilibrium of the immune system and averting overreactions. Asthma patients have been shown to have dysfunctional or reduced Treg counts, which suggests compromised immune control [12]. This might exacerbate asthma symptoms by triggering overreactions of the immune system to innocuous things like allergens. In autoimmune asthma, the cytokine network plays a critical role in regulating the immune response. Different immune cells produce small proteins called cytokines, which operate as messengers to facilitate cell-to-cell contact and coordinate immune responses.

Th2 cells generate IL-4, which is essential for stimulating the synthesis of IgE antibodies that cause allergic responses. Elevated IL-4 levels in asthma help to trigger Th2 responses, which in turn increase IgE production and eosinophil recruitment [13,14]. The development, activity, and survival of eosinophils—a particular subset of white blood cells implicated in allergic inflammation—are significantly influenced by IL-5. IL-5 encourages eosinophil immigration into the airways in autoimmune asthma, which damages tissue and exacerbates asthma symptoms [15].

Another significant cytokine that Th2 cells generate is IL-13. It contributes to the pathophysiology of autoimmune inflammatory responses in asthma and has a number of biological functions with IL-4. IL-13 stimulates eosinophil recruitment, mucus formation, and airway hyperresponsiveness [16]. Th17 cells are a subpopulation of T cells that primarily generate IL-17. IL-17 encourages the recruitment and activation of neutrophils, another kind of white blood cell, in autoimmune inflammatory responses in asthma. Tissue

injury and airway inflammation are exacerbated by neutrophils. Numerous immune cells generate the proinflammatory cytokine TNF-α. In asthmatic autoimmune inflammatory responses, it stimulates mucus production, airway remodeling, and airway inflammation [17]. Chronic airway inflammation, bronchial constriction, and other hallmarks of asthma are caused by the interaction and modulation of the immune response by these and other cytokines in autoimmune inflammatory responses. Th2 and Th17 responses are dysregulated in the complex cytokine network of autoimmune inflammatory reactions in asthma, which results in tissue damage and ongoing inflammation in the airways. Individual differences may exist in the existence of allergy biomarkers and dysregulated immune system responses in asthma, and further study is required to fully comprehend their significance in the condition. Table 1 lists important allergy indicators that are often linked to asthma and describes how each one contributes to the illness. The intriguing relationship between autoimmunity and allergy indicators in asthma is highlighted in this thorough analysis. Researchers and clinicians may learn a great deal about the pathophysiology, diagnosis, and therapy of these complicated illnesses by comprehending the common immunologic pathways and their clinical consequences.

2. Asthma and Inflammation

A major contributing element to asthma, a chronic respiratory disease characterized by airway swelling and tightness, is inflammation. When asthmatics are exposed to certain stimuli, such as allergens, irritants, or respiratory infections, their immune systems may respond, causing their airways to become inflamed. There are several elements involved in the inflammatory response in asthma. First, chemical messengers including histamine, leukotrienes, and cytokines are released by immune cells, especially mast cells and eosinophils. These chemicals enlarge blood vessels, produce more mucus, and contract the smooth muscle around the airways, which causes constriction of the airways and makes breathing harder. Asthma-related inflammation is categorized as eosinophilic and neutrophilic inflammation, a kind of chronic inflammation. An important part in allergic responses is played by eosinophils. They penetrate the respiratory tract's tissues and release more inflammatory chemicals, which feed the chain reaction and cause further respiratory tract damage [27]. Over time, airway wall remodeling may result from asthma's ongoing inflammation. Structural alterations include thicker airway walls, enlarged mucous glands, and greater collagen deposition are all part of this remodeling. Reduced lung function and airway constriction are additional effects of these alterations [28]. Reducing inflammation and avoiding or alleviating symptoms are the main goals of asthma treatment. Inhaled corticosteroid medicines, which assist decrease inflammation in the airways, are frequently used pharmaceuticals. T helper cells play a crucial role in regulating immune responses. Depending on the severity and course of therapy of the asthma, other drugs, bronchodilators, leukotriene modifiers, and monoclonal antibodies that target certain inflammatory components may also be suggested.

3. Asthma and Allergies

Although allergens are generally harmless for most people, allergies occur when the immune system reacts to them. Common allergies include dust mites, pollen, certain foods, bug stings, animal dander, and animal saliva. Allergy responses occur when an allergic person comes into contact with an allergen, which causes their immune system to release chemicals like histamine. Sneezing, itching, runny or stuffy nose, watery eyes, and skin rashes are typical symptoms of allergies, however they may vary according on the allergen and the person. The severity of allergic responses may vary, and in some situations, they can even result in potentially fatal anaphylaxis. Allergies and asthma are closely connected conditions, and people with asthma often have allergy triggers that exacerbate their symptoms. Allergies may exacerbate asthma symptoms, and many individuals with asthma also have them. An asthma attack or worsening of pre-existing symptoms may occur when a person with allergic asthma comes into contact with an allergen. Increased inflammation, edema, and mucus formation in the airways due to an allergic reaction may further constrict the airways and make breathing more difficult [29]. Controlling allergens is crucial to managing allergic asthma. Allergies are a common occurrence for asthma sufferers in Saudi Arabia and other parts of the globe. In this nation, the prevalence of allergic asthma is very high. The prevalence of asthma and its allergic variations in various regions of Saudi Arabia has been the subject of several studies [30, 31]. 2405 people participated in a cross-sectional study by Al Ghobain et al. (2018) utilizing the European Community Respiratory Health study (ECRHS) questionnaire. There were no discernible gender differences in the prevalence of wheezing over the previous 12 months without a cold ($p = 0.107$), which was 18.2%. 11.3% of participants reported having asthma that was diagnosed by a doctor; once again, there was no discernible difference between men and women ($p = 0.239$). Furthermore, 10.6% of respondents said they were on asthma medication. The region of residence ($p = 0.07$), educational attainment ($p = 0.11$), and smoking behaviors ($p = 0.06$) did not significantly vary between asthmatics and non-asthmatics. Nonetheless, a noteworthy correlation ($p < 0.001$) was discovered between nasal allergies and asthma. Using the ECRHS questionnaire, the research found that the prevalence of asthma is much greater than in most other nations [30]. Alqahtani (2016) said that over the last three decades, there has been a notable rise in allergy disorders, which has increased morbidity and mortality among children and young people. Finding out the frequency and risk factors of allergy illnesses in 1700 Saudi schoolchildren from Najran, in the southwest of the country, was the main goal of the research. Asthma prevalence was 27.5%, rhinitis prevalence was 6.3%, and atopic dermatitis prevalence was 12.5%. Among the risk variables that were found were pet ownership, fast food intake, proximity to trucks, and male gender. 42.5% of youngsters were found to be sensitized to allergens, with the most prevalent ones being home dust mites, grass pollen, and cat hair. In order to lessen the burden of allergy disorders, the research emphasizes the need of comprehensive intervention programs [31]. It has long been recognized that asthma and allergic rhinitis (AR) are comparable conditions.

Nonetheless, the most significant contributor to the pathophysiology of these two illnesses is the immune system. According to further study, the severity of asthma may cause an inflammatory reaction in the upper airways, raising the chance of AR.

4. The Asthma Cytokine Network

T helper cells play a crucial role in regulating immune responses. The cytokine network in asthma is a complex and dynamic system that is composed of immune cells, cytokines, and signaling pathways. Cytokines are microscopic proteins secreted by immune cells that are vital for regulating intercellular communication, immunologic responses, and inflammation. Table 2 provides a summary of the several cytokines linked to asthma as well as details on how each one affects the inflammatory and immune responses involved with the condition.

Asthma-related hyperreactivity, tissue remodeling, and airway inflammation are all mediated by cytokines. It's critical to keep in mind that our understanding of the asthma cytokine network is always changing, with fresh research often identifying novel nuances and possible therapeutic targets. diverse patients may also have diverse profiles, which might result in differences in responsiveness and cytokine expression. Consequently, customized therapy regimens are becoming more and more important for managing asthma [44].

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4.1. Th2 Cytokines

The immune system causes inflammation in asthma, which narrows the airways. Coughing, wheezing, chest constriction, and trouble breathing are some of the symptoms that arise from this. In asthma, cytokines such as IL-4, IL-5, and IL-13 often drive this immunological response. Asthma patients often have a high Th2 immune response [45]. A variety of cytokines released by these Th2 cells intensify inflammation and its associated symptoms. Th2 induction involves the following cytokines:

4.1.1. IL-4, or interleukin-4

The body's allergic responses, particularly allergic asthma, and associated illnesses are largely influenced by IL-4. The immune system's reaction to allergens is significantly influenced by this cytokine, which is mostly generated by Th2 cells. The development of Th2 cells, which are specialized to cause allergic responses and release cytokines like IL-5 and IL-13, is one of IL-4's primary roles. These cytokines encourage the development of mucus in the airways and facilitate the entry of eosinophils. Furthermore, B cells are guided by IL-4 toward plasma cells that generate antibodies, especially IgE. Because it binds to allergens and causes mast cells and basophils to generate pro-inflammatory chemicals after future allergen exposures, this particular antibody, IgE, is essential in allergic episodes [46]. These IgE antibodies are essentially produced by B cells in response to IL-4, which then triggers mast cells and basophils to identify certain allergens. Furthermore, IL-4 is linked to asthma's heightened airway sensitivity, which causes bronchial constriction in response to allergens or other irritants. In addition to IL-13, IL-4 causes the airways to produce more mucus, which may obstruct them and make breathing difficult. Prolonged exposure to IL-4 may potentially alter the airway's structure, making asthma more chronic.

4.1.2. IL-5, or interleukin-5

Particularly in instances of allergic asthma characterized by eosinophilic inflammation, IL-5 plays a significant role in the development of asthma. Eosinophil proliferation, differentiation, activation, and survival are all significantly regulated by IL-5. The generation of eosinophils in the bone marrow and their migration into the airways and other organs are strongly stimulated by IL-5. Elevated IL-5 levels in asthma contribute to airway inflammation by encouraging the buildup of eosinophils in the airway walls [47]. Numerous inflammatory mediators released by eosinophils have the potential to aggravate tissue damage and airway inflammation. These mediators have the potential to exacerbate bronchoconstriction and airway hyperresponsiveness, which may result in asthma symptoms. Eosinophils may also aid in the secretion and synthesis of mucus in the airways when IL-5 is present. Lung function may be hampered by increased mucus, which may further block the airways. Airway remodeling, which entails structural changes in the airway walls, may be exacerbated by prolonged exposure to eosinophils and their byproducts. This remodeling may contribute to the chronicity of asthma and cause long-term alterations in lung function [48]. Other Th2 cytokines including IL-4 and IL-13 are often generated with IL-5. Together, these cytokines intensify the allergic reaction, resulting in worsening symptoms and inflammation.

4.1.3. IL-13, or interleukin-13

A key cytokine in the development and progression of asthma, especially allergic asthma, is IL-13. It has several roles with IL-4 and is closely associated with the Th2 immune response. IL-13 is produced by a variety of immune cells, including Th2 cells, and has a major effect on the immune system and the airways. According to a research, IL-13 is a key factor in asthma as the main cause of airway inflammation [49]. It encourages the recruitment of inflammatory cells to the airways, including mast cells, T cells, and eosinophils. Asthma symptoms may arise from bronchoconstriction and airway hyperresponsiveness brought on by this inflammation. In the airway epithelium, IL-13 promotes the development of goblet cells that secrete mucus. Breathing becomes more difficult and exacerbates asthma symptoms when the airways are obstructed by increased mucus production. According to the research by Pope et al. 2001 [16], IL-13 is linked to airway remodeling, a process that is defined by structural alterations in the airway walls. Changes in blood vessel architecture, increased extracellular matrix protein deposition, and thickening of the smooth muscle of the airways might result from this. Over time, these alterations could contribute to ongoing airway blockage and declining lung function. Furthermore, the airway epithelial barrier, which typically acts as a barrier to keep out allergens and irritants, may be compromised by IL-13. Increased exposure to allergens and further inflammation may result from this barrier failure. Like IL-4, IL-13 stimulates the synthesis of IgE antibodies. IgE antibodies contribute to allergic reactions by making mast cells and basophils more sensitive to allergens, which causes them to produce inflammatory mediators. Fibroblast activation and the synthesis of collagen and other extracellular matrix components may result from prolonged exposure to IL-13. Structural alterations and airway remodeling are facilitated by this fibrotic response.

4.1.4. IL-9, or interleukin-9

Asthma development is linked to IL-9, namely its role in airway inflammation and heightened susceptibility [50]. Although IL-9 was first identified as a component that supported T-cell proliferation, its impact extends beyond this. It is essential for drawing in and triggering different immune cells in the airways, including T cells, mast cells, and eosinophils. Inflammatory chemicals released by immune cells contribute to airway inflammation and ultimately cause asthma symptoms to appear. In the mucosa of the airways, IL-9 promotes the development of goblet cells that produce mucus. Asthma symptoms might worsen and airway obstruction can result from increased mucus production. Inflammatory chemicals released by immune cells contribute to airway inflammation and ultimately cause asthma symptoms to appear. T helper cells play a crucial role in regulating immune responses. The respiratory tract mucosa's goblet cells, which produce mucus, proliferate and differentiate in response to IL-9. Asthma symptoms might worsen and airway obstruction can result from increased mucus output [51]. Asthma is characterized by increased airway sensitivity, which is exacerbated by IL-9. When certain triggers happen, this heightened sensitivity causes more noticeable bronchoconstriction and limited breathing. Eosinophils, which are often present in asthmatics' airways in higher quantities, are attracted to and activated by IL-9. Eosinophils may harm tissues and are implicated in inflammatory and allergic responses. Important immune cells that contribute to allergic responses, mast cells, may be stimulated by IL-9. Histamine and other chemicals that promote inflammation, mucus production, and constricted airways are released by these mast cells when they are triggered. Th9 cells, a particular subset of CD4+ T cells, produce IL-9. This cytokine increases the Th2 immune response often seen in asthma by collaborating with other Th2 cytokines including IL-4 and IL-13 [16,35,49].

5. T Helper Cell Subset Cytokines

5.1. IL-17, or interleukin-17

The Th17 response is the main immune response type that IL-17 is linked to. Although Th2 responses predominate in allergic asthma, certain asthma cases, especially those involving non-eosinophilic inflammation, have also been linked to Th17 responses and IL-17. The recruitment and activation of neutrophils in the airways is a hallmark of neutrophilic inflammation, which is often linked to IL-17. Eosinophilic inflammation, which usually occurs in allergic asthma, is different from this kind of inflammation. Airway blockage and airflow restriction may be exacerbated by neutrophilic inflammation. The recruitment and activation of neutrophils in the airways is a hallmark of neutrophilic inflammation, which is often linked to IL-17 [52]. Eosinophilic inflammation, which usually occurs in allergic asthma, is not the same as this kind of inflammation. Airway blockage and airflow restriction may be exacerbated by neutrophilic inflammation [53]. The cytokine IL-17 and Th17 cells induce neutrophilic inflammation in Th17 asthma, a subtype of asthma linked to more severe, steroid-resistant instances. People who smoke, have respiratory infections, are obese, or have been exposed to pollutants are at risk for Th17 asthma. There is a known Th2/Th17 overlap phenotype in which individuals have both Th2-mediated allergy reactions (eosinophilic inflammation) and Th17-driven inflammation (neutrophilic), even though Th17-driven asthma is often non-allergic. Treatments that target both the Th2 and Th17 pathways are necessary because of this overlap, which causes more severe asthma that is often resistant to conventional therapy [54,55,56].

5.2. TNF-α, or tumor necrosis factor-alpha

Among the cytokines that cause the acute phase response is TNF-α, a proinflammatory cytokine that is essential for systemic inflammation. TNF-α is mostly produced by macrophages, although it may also be produced by CD4+ lymphocytes, Nk cells, neutrophils, mast cells, eosinophils, and neurons [57]. Asthma, a chronic inflammatory lung illness marked by bronchoconstriction, airway inflammation, and elevated airway sensitivity, is linked to TNF-α [58]. TNF-α has a complex role in asthma and disrupts a number of systems. TNF-α may cause endothelial cells to exhibit more adhesion molecules, which increases leukocyte entrance into the airways. Substances that worsen inflammation are subsequently released by these leukocytes. Increased airway sensitivity and bronchoconstriction may result from TNF-α's ability to further trigger the production of inflammatory chemicals. Since there are several forms and phenotypes of asthma, the impact of TNF-α may vary depending on these variances. Furthermore, not all asthmatic patients respond well to TNF-α targeted therapy. Therefore, further research is necessary to determine whether individuals may benefit from anti-TNF-α therapy.

5.3. IFN-γ, or interferon-gamma

IFN-γ, which is primarily generated by natural killer cells and activated T cells, is essential for immunological responses. It takes part in a number of immune-related processes, including immune response control, macrophage activation, and antigen presentation enhancement [59]. In some situations, IFN-γ may have both pro- and anti-inflammatory actions. IFN-γ has a variety of roles in asthma, a chronic lung illness characterized by airway inflammation, bronchoconstriction, and airway hyperreactivity. In general, there are two types of asthma: eosinophilic and non-eosinophilic [60]. The Th1 response, which is more prevalent in non-eosinophilic asthma, is associated with IFN-γ. It is possible that IFN-γ has a protective role in non-eosinophilic asthma. The Th2 response, which is linked to eosinophilic inflammation, may be offset by the Th1 response. IFN-γ may lessen eosinophilic inflammation, which is linked to asthma flare-ups, by promoting a Th1 response [44]. Furthermore, it has been shown that IFN-γ inhibits mast cells' production of pro-inflammatory mediators like histamine. But with asthma, too much IFN-γ production might be detrimental. Airway remodeling, a feature of chronic asthma that results in structural alterations to the airways, has been linked to elevated IFN-γ levels. Reduced lung function and increased airway hyperresponsiveness may be the outcomes of these changes. IFN-γ's function in asthma is still being investigated, and there is continuous curiosity in how this cytokine interacts with other immune mediators in the asthmatic setting. Future treatments for asthma could focus on developing medications that target IFN-γ or alter the ratio of Th1 to Th2 responses. However, these treatments need to be carefully crafted to avoid unintended side effects or a worsening of inflammation.

6. Cytokines that regulate

In a number of illnesses, including asthma, regulatory cytokines play a critical role in the immune response. Wheezing, coughing, and dyspnea are symptoms of asthma, a chronic inflammatory disease that affects the pulmonary airways [43]. An important factor in the onset and aggravation of asthma symptoms is the immune system's reaction to allergens or other triggers. Immune cells and other body cells emit tiny proteins called cytokines, which aid in coordinating the immune response. Cytokines may be classified into a number of distinct categories, such as regulatory and pro-inflammatory. The immune response is modulated by regulatory cytokines, which may aid in tissue repair and inflammation reduction in asthma [61]. The following are the main regulatory cytokines implicated in asthma:

6.1. IL-10, or interleukin-10

A regulatory cytokine called IL-10 has the ability to reduce inflammation and prevent certain immune cells, such T cells and macrophages, from activating and functioning. Pro-inflammatory cytokines and other inflammatory mediators may be produced less often when IL-10 is present [62]. IL-10 may prevent immune cells like macrophages from releasing inflammatory cytokines including TNF-alpha, IL-6, and IL-1. As a consequence, inflammation is decreased. T cells, B cells, and macrophages are examples of immune cells whose activation may be reduced by IL-10. As a result, inflammation is decreased along with the immunological response. Treg development and activity may be enhanced by IL-10, which aids in reducing inflammation and averting autoimmune responses [39]. In order to counteract the effects of proinflammatory cytokines and maybe improve asthma, IL-10 is essential.

6.2. TGF-β, or Transforming Growth Factor-Beta

TGF-β is a crucial cytokine that controls the immune system, inhibits the development and activation of certain immune cells, and aids in tissue healing. However, asthma-related airway alterations, such as structural abnormalities and increased airflow resistance, may be linked to overproduction of TGF-β. Additionally, it plays a key role as a mediator in tissue healing and immunological response. Numerous facets of the illness have been linked to TGF-β [36,63]. Changes in the structure of the airway walls, known as airway remodeling, are a hallmark of persistent asthma. This change involves new blood vessel creation, smooth muscle expansion,

and thickening of the subepithelial area. TGF-β contributes to this process by encouraging the proliferation of fibroblasts and the buildup of extracellular matrix elements, which causes the subepithelial layer to thicken. Furthermore, TGF-β has the ability to affect smooth muscle cell growth. Epithelial–Mesenchymal Transition (EMT) is believed to have a role in asthmatic airway remodeling or alterations that might result in thickening of the airway walls, which hinders airflow and lowers lung efficiency [64]. By prompting these epithelial cells to undergo EMT, which results in the loss of their original features and the acquisition of mesenchymal traits, TGF-β plays a critical role in this process. This enhances the cells' capacity to move and invade in addition to increasing the synthesis of extracellular matrix components. One characteristic of persistent asthma is airway remodeling, which is significantly influenced by TGF-β. Subepithelial fibrosis, or thickening of the airway walls, may result from its stimulation of EMT. Furthermore, TGF-β has the ability to stimulate fibroblast transformation and proliferation, which is a contributing factor to airway fibrosis. The intricate nature of asthma is exacerbated by the interplay between EMT and TGF-β, which highlights the interdependence of cell transformation and regulatory factors [41,65]. Further investigation into this connection might lead to improved treatment approaches in the future.

6.3. IL-35, or interleukin-3

A recently discovered regulatory cytokine, IL-35, has the potential to be useful in managing immunological responses in asthma because of its capacity to suppress T-cell activation and lower the production of inflammatory cytokines [66]. Because of its immunosuppressive properties, it is being investigated as a potential treatment target for autoimmune and inflammatory conditions, such as asthma. However, in order to create focused and efficient therapies for asthma, a better knowledge of the intricate function that regulatory cytokines play in the condition is necessary.

7. Immune System Dysregulation in Asthma

When the immune system mistakenly attacks and damages the body's tissues, cells, or organs, it is known as a dysregulated immune system. While asthma is best understood as a long-term respiratory disease marked by inflammation and constriction of the airways, there is continuous investigation and speculation about possible autoimmune pathways that may affect some features of asthma [67]. Certain autoantibodies are often used as distinct indicators of autoimmune disorders. A potential connection between autoantibodies and asthma, a primary inflammatory illness of the airways, has drawn increasing attention recently [68,69,70,71]. According to certain study, autoantibodies may be present in asthmatic individuals, and in some situations, these antibodies may contribute to the disease's underlying causes. Autoantibodies that target bronchial epithelial cells have been found in certain asthmatic individuals. Asthma-related epithelium damage and dysfunction may be exacerbated by such autoantibodies. Furthermore, there is evidence to imply that people with severe asthma may have higher levels of these autoantibodies or that their effects may be more pronounced than those with milder forms of the condition.

One kind of immune cell that contributes to autoimmune responses is called a Th17 cell. They produce cytokines that cause inflammation. Patients with asthma, particularly those with severe or steroid-resistant symptoms, have higher levels of Th17 cells and the cytokines they release in their airways [72,73,74]. Treg cells play a vital role in controlling the immune system and averting autoimmune diseases. The onset and subsequent severity of asthma may be influenced by the dysfunction of these cells. The onset and course of asthma are significantly influenced by immune system dysfunction.

An imbalance in the immune response that leads to an elevated inflammatory response and heightened airway sensitivity is known as immunological dysregulation in asthma [12]. An important immunological imbalance linked to asthma is linked to an increased Th2 immune response. A subgroup of T cells called Th2 cells are in charge of releasing a number of cytokines, including IL-4, IL-5, and IL-13. Asthma's hallmark symptoms are caused by these cytokines, which also encourage the development of allergic inflammation, mucus formation, and eosinophil deposition in the airways. The hallmark of asthma is immune system dysregulation, which results in a higher concentration of eosinophils in the airways, producing inflammation and tissue damage. This kind of inflammation is often linked to allergic asthma [27].

Airway remodeling is the term for the structural alterations in the airways that might result from an immune system imbalance over time. Airway smooth muscle cell alterations, thickening of the airway walls, and increased mucus production are all examples of this phenomena. Reduced lung capacity and ongoing airway blockage may result from such alterations. Immune signaling relies heavily on cytokines. The generation of cytokines is unbalanced in asthma. For instance, whereas lower levels of regulatory cytokines like IL-10 result in insufficient regulation of inflammation, elevated levels of IL-4, IL-5, and IL-13 encourage the Th2-mediated allergic response [75,76,77]. Asthma is also linked to the innate immune system, which offers quick but general reactions to pathogens and antigens. Immune cells' pattern recognition receptors (PRRs) may cause inflammation by identifying certain molecular patterns in pathogens [78,79,80,81]. Even when there is no infection, PRRs may lead to increased inflammation in asthma. Conversely, the antibody class IgE is implicated in allergic reactions [82,83]. IgE antibodies against innocuous items may be produced as a result of immunological dysregulation in asthma, which can cause allergic responses and aggravate airway

inflammation. Histamine, leukotrienes, and other inflammatory mediators are released by mast cells, basophils, and other immune cells, contributing to asthma. Asthma causes dysregulation of this immune cell activation, which exacerbates inflammation and bronchoconstriction [84].

Recent Studies and Future Scope

Asthma should aim to unravel the intricacies of immune system dysregulation and its variable phenotypic expressions, particularly in steroid-resistant and autoimmune subtypes. A major priority is the development of personalized medicine based on immunophenotyping, enabling clinicians to match patients with the most effective biologic therapies targeting specific cytokines or immune cells. With increasing evidence linking autoantibodies and T-cell imbalances to asthma severity, deeper exploration into autoimmune mechanisms could identify novel diagnostic markers and treatment targets. Moreover, advancements in genomics and epigenetics can help identify risk factors at the molecular level, guiding early intervention and preventive strategies in at-risk populations. Innovative diagnostic tools, such as multiplex cytokine assays and integrated biosensors for FeNO, IgE, and eosinophils, are expected to enhance precision in asthma monitoring. Future clinical trials should also explore the therapeutic potential of IL-35, TGF-β modulators, and inhibitors of epithelial–mesenchymal transition to mitigate airway remodeling. Additionally, environmental studies focusing on allergen control, urban pollution, and microbiome modulation may offer holistic strategies to reduce asthma prevalence and improve quality of life. Incorporating artificial intelligence and machine learning into asthma management could revolutionize symptom tracking, predictive modeling, and treatment adherence. Ultimately, interdisciplinary collaboration among immunologists, pulmonologists, geneticists, and public health experts is essential to translate these research advancements into clinical practice and public health policy. Through such efforts, we may not only treat but potentially prevent or reverse the course of asthma in the future.

Table 1: shows the recent studies in the field of asthma.

Study/Report Title	Year	Main Focus	Key Findings/Advances
CAR T cells in Asthma	2024	Immunotherapy	CAR T cell technology is being adapted to suppress asthma by targeting immune pathways [85].
Distinctive Lung Macrophages	2024	Immunology	CD39+CD9+ lung interstitial macrophages suppress IL-23/Th17-mediated neutrophilic asthma by inhibiting NETosis [85].
Benralizumab for Asthma Attacks	2024	Biologic Therapy	Benralizumab, previously for severe cases, could be used routinely for ~2 million asthma and COPD attacks annually in the UK, marking the first major advance in 50 years [86].
Injectable Antibody Therapy Clinical Trial	2024	Targeted Therapy	Ongoing trial for an antibody injection aimed at reducing airway inflammation and asthma symptoms, with hopes for fewer injections and improved quality of life [86].
GINA 2024 Report	2024	Global Guidelines	Updated global asthma management and prevention strategies based on new scientific evidence, including medication dose clarifications [87].
ANANKE Study: Benralizumab Effectiveness	2024	Biologic Therapy	Demonstrated sustained effectiveness of benralizumab in both biologic-naïve and experienced severe eosinophilic asthma patients [88].
SINA 2024: Saudi Asthma Guidelines	2024	Clinical Guidelines	Emphasizes personalized medicine, new biologics, and evidence-based updates, including the management of asthma during respiratory infections [89].
Personalized Approaches in Asthma Management	2024	Precision Medicine	Integration of personalized treatment reflecting disease heterogeneity, especially with new biologic agents [89].
Immunological Mechanisms in Asthma	2024	Basic Research	Advances in understanding immune cell roles (e.g., Th17, NETosis) in asthma pathogenesis, guiding new therapeutic targets [90].
Strategic Treatment Based on Inflammation Patterns	2024	Clinical Strategy	Recognition of distinct inflammation patterns allows for more strategic, individualized treatment delivery [90].

Conclusion

Asthma remains a complex and multifactorial respiratory disorder, deeply rooted in immune dysregulation and hypersensitivity responses. The involvement of diverse T-helper subsets, cytokine storms, and eosinophilic or neutrophilic inflammation underlines the heterogeneity of this condition. A significant shift in understanding has emerged with the recognition of autoimmune components in asthma pathogenesis, especially in severe or steroid-resistant cases. Cytokines such as IL-4, IL-5, IL-13, and IL-17 orchestrate inflammatory cascades that result in bronchial hyperresponsiveness, mucus overproduction, and airway remodeling.

Simultaneously, a deficit or dysfunction in regulatory cytokines like IL-10 and TGF-β compromises immune tolerance, perpetuating chronic inflammation. The interplay between allergic triggers and immune cells amplifies this cycle, posing challenges for effective disease control. Conventional treatments, including corticosteroids and bronchodilators, offer symptom relief but fall short in modifying the underlying immune dysfunction in many patients. The use of monoclonal antibodies targeting specific immune pathways marks a promising advancement, yet access, cost, and variability in response remain concerns. Moreover, regional studies, such as those in Saudi Arabia, emphasize the critical role of environmental and genetic factors in disease prevalence. A comprehensive approach integrating immune profiling, environmental management, and personalized medicine is essential. By advancing our understanding of the immunopathology of asthma and developing targeted therapies, it is possible to shift from generalized management toward precise, individualized care. This paradigm shift holds the potential to significantly reduce disease burden and enhance the quality of life for millions of asthmatics worldwide.

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