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Interleukin 17 gene in Bronchial Asthma: Review Article

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ABSTRACT

Background: Asthma patients from all walks of life share a common symptom: persistent airway inflammation. A history of wheezing, chest tightness, shortness of breath, and cough, along with these symptoms, are diagnostic of this condition. Serum levels of interleukin-17 (IL-17) were considerably higher in patients with uncontrolled asthma compared to those with managed asthma and healthy people.

Objective: To study and focus on role of IL-17 among bronchial asthma patients.

Methods: We scoured medical papers and databases including PubMed, Google Scholar, and Science Direct for information on IL-17 and bronchial asthma. Only the most recent or comprehensive studies conducted between November 2006 and December 2022 were included in the analysis. The authors also assessed the usefulness of references drawn from similar books. Documents written in languages other than English have been neglected because of a lack of funding to translate them. Unpublished articles, oral talks, conference abstracts, and dissertations were all generally agreed upon not to constitute valid scientific investigation.

Conclusion: Genetic research, clinical correlations, in vitro investigations, and animal models all point to IL-17 dysregulation as a possible cause of asthma. Asthma is linked to variations in the IL-17 gene in humans. Based on in vitro studies revealing that IL-17 A caused IL-17 receptor alpha expression in human bronchial epithelial cells, the notion was initially proposed that IL-17 A caused airway neutrophilia, a trait of the neutrophilic phenotype.

Keywords: Bronchial asthma, IL-17.

INTRODUCTION

Asthma patients from all walks of life share a common symptom: persistent airway inflammation, wheezing, chest tightness, shortness of breath, and cough, which are hallmarks of this condition, as are histories of these and other respiratory symptoms **(1).**

Description of Asthma:

Worldwide, 1-18% of the population has asthma, making it the most prevalent chronic respiratory condition. Asthma is characterised by fluctuating wheezing, shortness of breath, chest tightness, and/or coughing symptoms and fluctuating expiratory airflow limitation. Exercising, being exposed to allergens or irritants, a shift in the weather, or a viral respiratory illness are all common triggers for these shifts. Sometimes, weeks or months will go by without any signs of the condition at all, and sometimes, symptoms and airflow limitation will disappear on their own or in response to medicine. On the other hand, persons with asthma might have episodes of worsening symptoms (exacerbations) that pose a serious risk to their health and the health of their community**.** Asthma is characterized by airway hyperresponsiveness to both direct and indirect stimuli and by persistent airway inflammation. These characteristics typically continue even in the absence of symptoms or abnormal lung function, however they may return to normal with treatment **(1).**

Epidemiology and Incidence:

More than 300 million individuals around the world, including 25 million Americans, suffer from asthma. Youngsters all throughout the world, including an estimated 6.4 million children in the United States, suffer from it. Asthma varies in incidence, severity, and fatality rates among regions. Asthma prevalence has been on the rise in some affluent countries, but seems to have levelled off in others, and the rate of increase varies widely depending on where you look. Asthma is more prevalent in males than females in both childhood and adulthood, suggesting that sex hormones may contribute to the development of various forms of the disease **(2)**.

Exposure to exogenous factors, such as cigarette smoke, a decrease in host resistance, an increase in the incidence of viral respiratory infection, allergens, cockroach allergy, and dietary changes, may explain the rise in the prevalence of paediatric asthma. These factors may reduce natural antioxidant defences, making the respiratory system more vulnerable to the oxidant injurious effects of free radicals **(3).**

More than a third of youngsters in some developed nations suffer from asthma or allergies, which has reached an alarming level. Whether this is attributable to a truly rising asthmatic and allergic population or just due to improved detection and diagnosis is unclear **(4).**

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The prevalence of asthma in the Middle East has recently climbed to between 5 and 23%, despite previous reports of it being lower than in Western countries. Sadly, in many underdeveloped countries, the prevalence of asthma had not been accurately identified due to a lack of high-quality epidemiological investigations. The rates can change by as much as 30% from one region to another, and from one set of research methods to another [(5)].

Etiology of bronchial asthma:

Guidelines issued by the Global Initiative for Asthma (GINA) list host and environmental variables as contributors to the disease [(1)].

Genetic:

More interactions with epigenetic exposures increase disease development, persistent bronchial inflammation, and tissue injury, all of which contribute to asthma's inherent nature, can cause pathologic changes and remodeling of the airway wall [(6)]**.** The term "epigenetics" refers to the study of heritable mechanisms that modify gene expression but do not alter the underlying nucleotide sequence of DNA. In humans, epigenetic mechanisms include post-transcriptional histone modifications, non-coding RNAs (including siRNA and miRNA), and DNA methylation (Figure 1) [(7)].

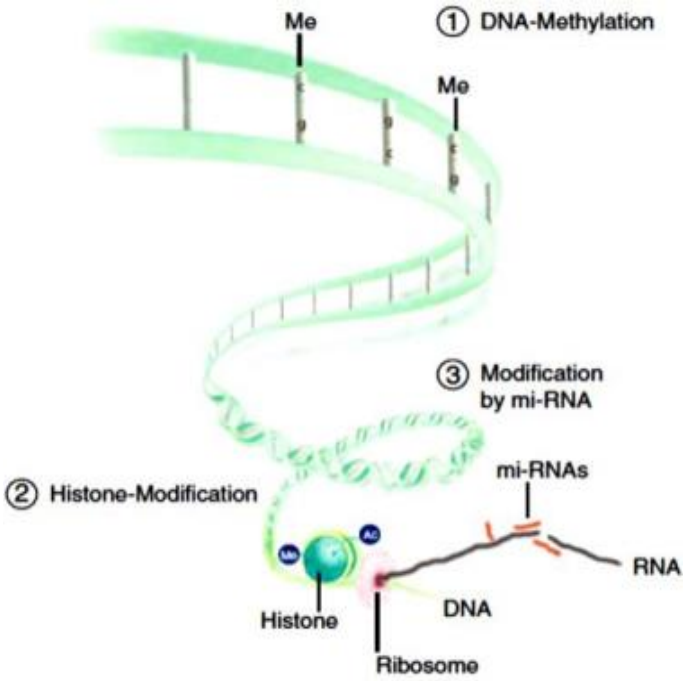

Figure (1): Epigenetic mechanisms in humans.

There is a three-dimensional organisation to the genome. DNA has a nucleotide structure called an alpha helix. Methylation of cytosines alters the DNA double helix structure, making it more difficult for transcription factors to bind to the DNA. Nucleosomes comprise eight histone proteins (42) and 146 base pairs of DNA to further arrange the DNA. DNA accessibility at the location of these nucleosomes is altered when histones are methylated or acetylated. Three, mi-RNA can interfere with mRNA transcription to control how efficiently it's transcribed into protein [(8)]**.**

While everybody is at risk for developing asthma, the condition most commonly manifests in preschool-aged children. In youngsters, between 50 and 80% of cases of asthma manifest themselves before the age of five. Asthma is more likely to persist if it is diagnosed at a younger age. Chronic asthma at age of 22 was predicted to be 7 times more likely if asthma began before age of 6 and 14 times more likely if wheeze persisted throughout childhood in the Tucson Children's Respiratory Study. The likelihood of long-term asthma decreased by 11% for every year that asthma was present before the age of 18**.** Several theories have been put out to explain the correlation between obesity and asthma. These include a shared genetic susceptibility, alterations in lung growth and mechanics, the existence of a systemic inflammatory process, and an increase in the prevalence of co-morbid illnesses. Asthma patients who are overweight or obese should consider losing weight as part of their treatment plan [(9)]**.**

Pathogenesis of asthma (Figure 2):

Asthma is characterised by recurrent airflow limitation due to multiple airway changes, including bronchial hyperreactivity, mucus overproduction, airway wall inflammation and remodeling, and airway narrowing. These changes are brought about by the coordinated actions of innate and adaptive immune cells with epithelial cells [(10)]**.**

Airway Inflammation in Asthma:

Activated mast cells, eosinophils, and T-lymphocytes are only a few of the many cells and biological factors involved in bronchial asthma. Eosinophils, neutrophils, and epithelial cells can be attracted and activated with the help of these cytokines. Eosinophil recruitment appears to require chemokines secreted by lymphocytes and epithelial cells, such as eotaxin and controlled upon activation of normal T-cell that are expressed and released [(10)]**.**

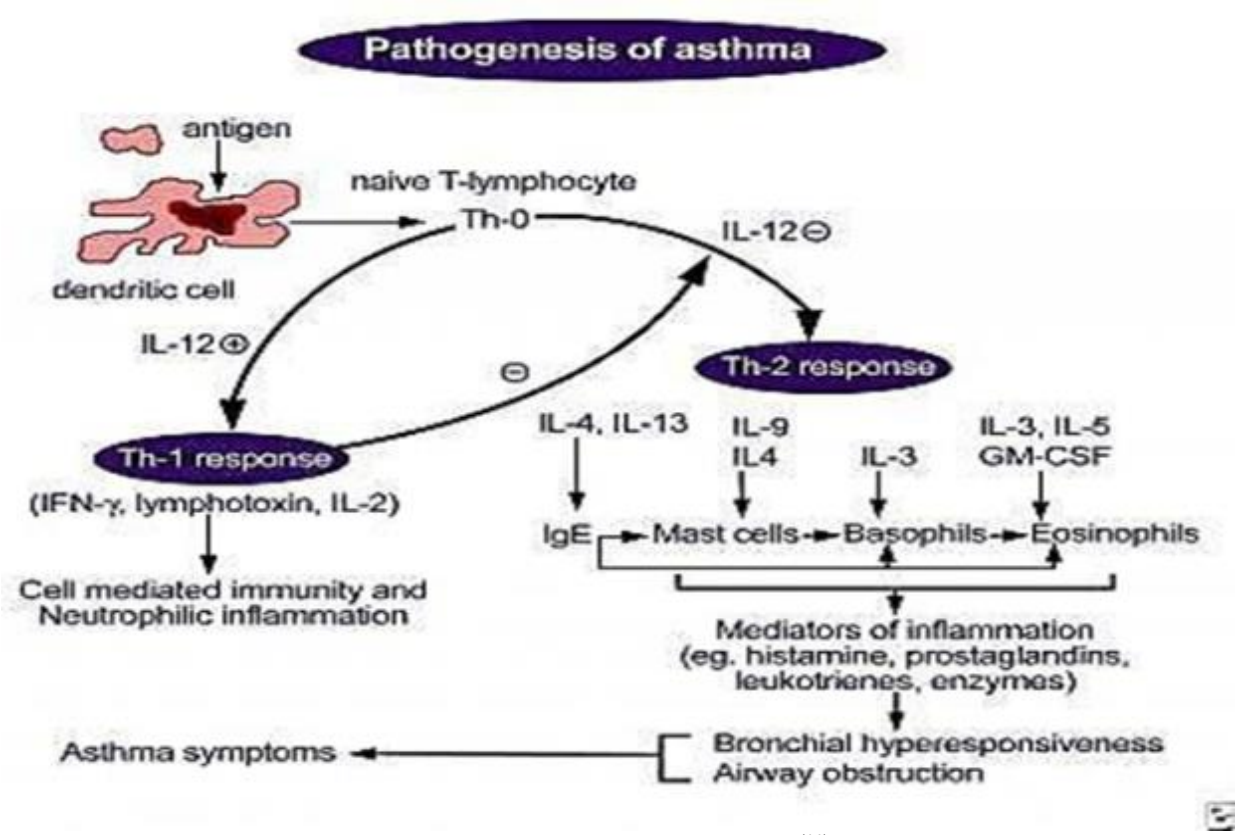

Figure (2): Asthma pathogenesis [11].

Inflammation of the airways and asthma symptoms result from a chain reaction that begins with antigen presentation by dendritic cells and continues with a lymphocyte and cytokine response. Both allergic and nonallergic bronchial asthma involve inflammation involving eosinophils. Adaptive immunity cells like Th2 cells and innate immunity cells like natural killer cells and type 2 innate lymphoid cells all play a role (ILC2) [12]. The absence of T cell and B cell receptors distinguishes innate lymphoid cells as a distinct subset of innate immune cells [13].

Inflammatory cells in asthma:

Eosinophilic asthma:

There are many eosinophils compared to other white blood cells. During asthma, IL-5 produced by Th2 cells induces the development of these cells from CD34+ pluripotent progenitor cells in the bone marrow. The bone marrow, blood, and tissue stages make up their entire life cycle [14].

Eosinophils are present throughout the body and may aid in tissue and immunological homeostasis in locations outside the digestive system, breasts, lungs, and bone marrow. Eosinophils have their own special chemokine receptors too. Eotaxin and monocyte chemotactic protein are two examples (MCP). These chemokines are thought to play a significant role in stimulating eosinophil accumulation in tissues. In children with allergies and asthma, there is an increase in plasma eotaxin. It was discovered to be significantly higher during an asthma episode. They were linked to eosinophils in the periphery of the blood and to IgE in the blood serum [15].

Activation of Th2 cells:

Dendritic cells in the airways respond to stimuli by secreting IL-4 and OX40 ligand, which promotes the differentiation of T cells into Th2 cells. Mast cells and basophils respond to IL-4 from Th2 cells by releasing histamine, leukotrienes, and cytokines, which in turn trigger asthma symptoms. The high affinity Fc receptors (FcRI) on mast cells and basophils are the targets of IgE, which is produced by B cells (Figure 3) [16].

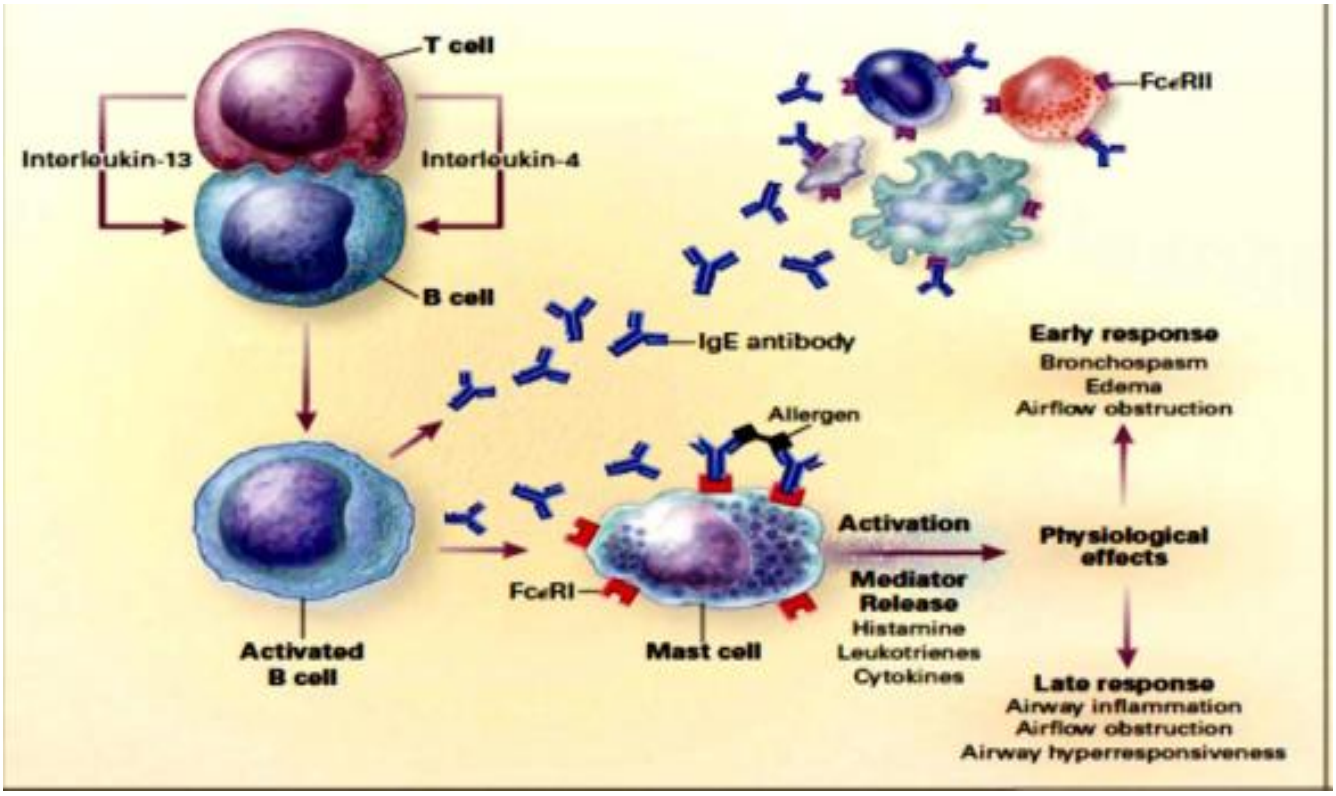

Figure (3): Important in IgE formation are interactions between CD4 T cells and B cells [(16)].

They have the ability to act as antigen-presenting cells (APC) within the airway lumen and then migrate to regional lymph nodes, where they can activate responses of CD4+T cells [(15)]**.** Eosinophils, when activated secrete granule proteins and inflammatory mediators including leukotrienes that damage airway tissues and granulocyte-macrophage colony-stimulating factor (GMCSF) that helps them stick around and keeps the inflammation going (Figure 4) [(17)]**.**

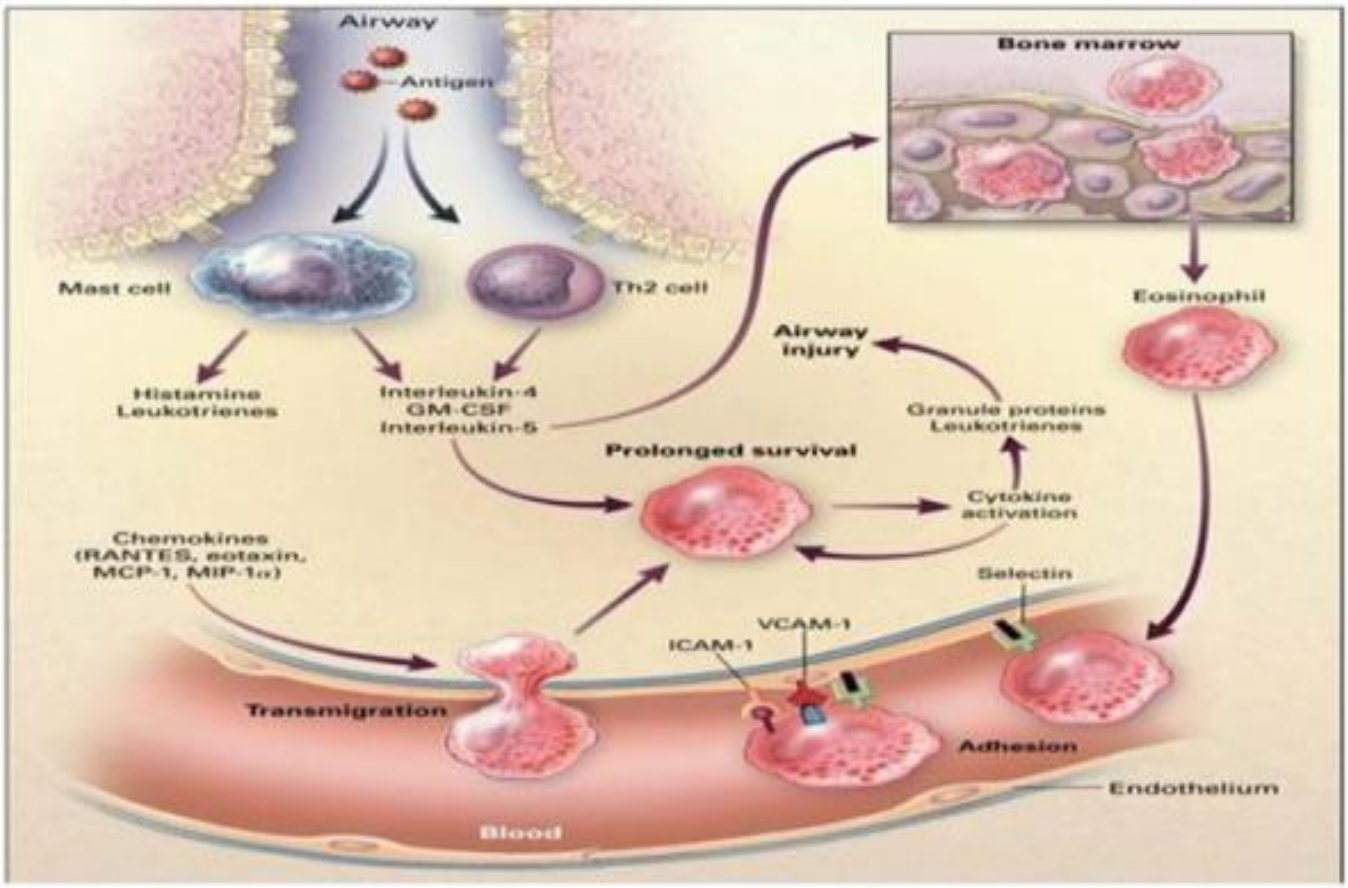

Figure (4): Inflammation caused by allergens and the role of eosinophils [(17)].

Neutrophilic asthma:

Individuals with mild to moderate chronic asthma do not appear to have a preponderance of neutrophils in their airways. Nonetheless, there appears to be an excess of neutrophils in the airways and induced sputum of patients with severe asthma. The airways of persons who die suddenly from asthma contain a high amount of neutrophils**.** Asthma caused by neutrophils could indicate a mechanism independent of T2. Possible link to Th17 cells' IL-17 production [(17)].

IL-17 isn't the only cytokine produced by Th17 cells that helps recruit neutrophils to the airways; IL-8, IL-21, IL-22, IL-26, TNF-, and granulocyte-monocyte colony-stimulating factor (GMCSF) are all involved as well. Cell-mediated immunity and phagocyte-dependent protective responses rely on Th1 cells, which are induced to mature by IL-12. Increased airway neutrophils and more severe asthma are both outcomes of increased Th17 cells, which in turn require TGF-1, IL-6, IL-1, and IL-23 for proliferation [(14)]**.** However, T regulatory (Treg) cells play a significant role in allergic asthma due to their ability to decrease effector cells through the inhibition of airway hyperresponsiveness (AHR) and Th2-mediated airway inflammation via the production of IL-10**.** Due to mucosal oedema and the production of pathological intraluminal mucus, as well as concentric smooth muscle contraction. Airway inflammation causes airway narrowing (Figure 5) [(18)]**.**

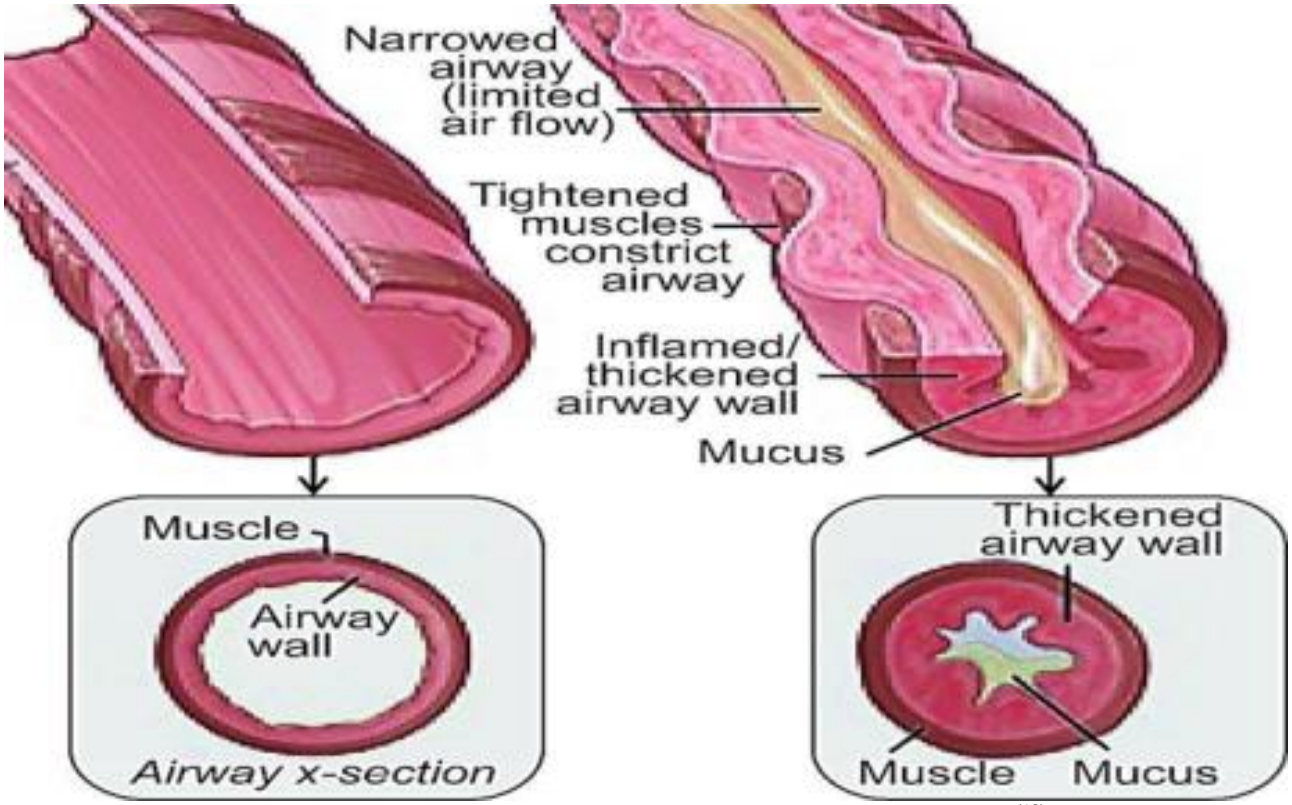

Figure (5): Asthma's airway restriction mechanisms are complex [(18)].

Airway remodeling in asthma:

Among the various cellular and molecular components of the bronchial wall, airway remodeling in asthmatic people is a complex multicellular process that results in structural changes. Asthma is characterized by seemingly endless cycles of tissue damage and healing, which may or may not involve remodeling. A working hypothesis that structural modifications can lead to the development of persistent airway hyper reactivity and fixed airway blockage in asthma, despite a lack of definitive information on how distinct remodeling aspects affect lung function in the disease [18].

Reduced lung function in asthma patients has been linked to a number of structural abnormalities, including inflammation of the airways, epithelial damage, subepithelial fibrosis, hyperplasia of the airway smooth muscle, hypertrophy and hyperplasia of the goblet cells, and angiogenesis. However, the timing and intensity of their manifestations vary from person to person [19].

Mediators and mechanisms of asthmatic remodeling:

Subepithelial fibrosis is the most talked about aspect of the redesigned airway, yet it is only one of many. However, systemic inflammation can result in detrimental host metabolic and hemodynamic abnormalities. Therefore, the immune system has developed anti-inflammatory mechanisms to minimise tissue damage and preserve or restore tissue homeostasis by working against the generation of pro-inflammatory chemicals [19]. Secreted proteins called interleukins (ILs) attach to their respective receptors and facilitate communication amongst leukocytes. They're a heterogeneous collection of cytokines and growth factors that leukocytes secrete [20].

Interleukins Families:

Sequence similarity and similarities in receptor chain activity are used to classify ILs into their respective families. Different types of effector T cells, including Th1, Th2, Th9, Th17, and T-follicular effector cells, can develop from CD4 naive T cells. These T-cell subsets can drive distinct inflammatory responses due to their unique cytokine profiles, chemokine responses, and cell-cell interactions. Effector Th2 cells release IL-4, IL-5, IL-9, and IL-13 as allergic illness progresses [20].

It is generally agreed that IL-17 cytokines play a significant role in defending against microbial invasion via the recruitment of neutrophils and the production of antimicrobial peptides, and in keeping the epithelial surface barrier intact [21]. Increased IL-17 expression and activity have been linked to genetic polymorphisms in the IL-17A and IL-17F cytokines, which play an important role in the activity of interleukins [22]. High levels of IL-17 are produced by individuals with the IL-17A rs2275913; G197A polymorphism in the cytokine promoter region, which in turn enhances IL-17-mediated immune responses. Up-regulation of IL-17F is also associated with the rs763780; A7488G polymorphism in the IL-17F gene's coding region [23].

Interleukin-17 and cancer lung:

Among the many types of cancer, non-small cell lung cancer (NSCLC) is one in which IL-17A SNPs have been demonstrated to affect IL-17A expression and, by extension, cancer risk. Previous studies on SNPs and somatic mutations in cancer were undertaken independently [24].

The connection between genetic variations and somatic mutations has been the subject of current works in cancer development research. The telomerase reverse transcriptase (TERT) SNP rs2736100 has been associated to EGFR mutation susceptibility in non-small cell lung cancer (NSCLC) [25].

IL-17 in asthma:

Patients with uncontrolled asthma had far greater serum IL-17 levels than individuals with managed asthma or healthy controls. Asthma sufferers' airways contain IL-17A and IL-17F, and their levels of expression are correlated with the severity of their disease [26].

Despite the identification of several variants in the IL-17A gene, the role that these variations play in the immunological and inflammatory response to various disorders remains unknown. As rs2275913 is found in the 5' regulatory region of the IL-17A gene, close to a binding motif for the nuclear factor activated T cells (NFAT), a critical regulator of the IL-17A gene promoter, it has been the subject of research. Individuals carrying the A allele generated more IL-17A and exhibited higher NFAT promoter affinity [27].

Genetic research, clinical correlations, in vitro investigations, and animal models all point to IL-17 dysregulation as a possible cause of asthma. Asthma is linked to variations in the IL-17 gene in humans. More CXCL8 mRNA was generated in vitro by IL-17A-treated human bronchial epithelial cells, and this neutrophil chemoattractant is more proof that IL-17A plays a role in airway neutrophilia. Some examples of early evidence linking IL-17A and human asthma include an increase in IL-17A+ cells in bronchoalveolar lavage BAL and sputum of 11 people with asthma compared to 7 healthy controls and a reduction in IL-17A-induced IL-6 release from airway fibroblasts when treated with dexamethasone in vitro. Despite the lack of statistically significant differences between asthmatics and healthy people, sputum IL-17A and airway hyperresponsiveness (AHR) may be inversely connected [28].

Severe asthma is associated with an increase in IL-17 generating T cells. A larger number of IL-17-secreting ILC3s were found in the sputum of individuals with severe asthma, according to another study [29, 30]. However, the findings of these small studies regarding such minor clinical relationships have not been

routinely repeated. We were unable to detect elevated levels of IL-17A protein in serum, sputum, or BAL from 84 healthy volunteers who underwent bronchoscopy for asthma [(31)]. Asthma exacerbations cause significant morbidity and death, and research suggests that Th17 cells have a role in both the viral aetiology and the resulting neutrophilic inflammation. Serum IL-17 is increased in children with asthma who are exposed to diesel fumes. IL-17A and neutrophilic inflammation are increased in those who smoke cigarettes [(32)].

One study identified a correlation between IL-17F+ cells in the bronchi and both airway neutrophils and the frequency with which asthma attacks flared up. IL-17F also co-localized with Th and cytotoxic T-cells [(33)].

CONCLUSION

Genetic research, clinical correlations, in vitro investigations, and animal models all point to IL-17 dysregulation as a possible cause of asthma. Asthma is linked to variations in the IL-17 gene in humans. The original notion linking IL-17A to airway neutrophilia, a characteristic of the neutrophilic phenotype, was based on in vitro research showing that IL-17A promoted the expression of IL-17 receptor alpha in human bronchial epithelial cells.

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Competing interests:

Nil.

REFERENCES

1. **Global Initiative for Asthma (2022):** Global strategy for asthma management and prevention. Pp: 1-225. https://ginasthma.org/gina-reports/
2. **Dharmage S, Perret J, Custovic A (2019):** Epidemiology of asthma in children and adults. Front Pediatr., 7: 246-52.
3. **El-Mashad G, Mahmoud A, Hafez A (2016):** The prevalence of bronchial asthma among primary school children in Menoufiya Governorate (El-Bagour Center): Menoufia Medical Journal, 29 (1): 89. DOI:10.4103/1110-2098.178992
4. **Mirzaei M, Karimi M, Beheshti S *et al.* (2017):** Prevalence of asthma among Middle Eastern children: A systematic review. Medical Journal of the Islamic Republic of Iran, 31: 9-13.
5. **Al-Hajjaj M (2008):** Bronchial asthma in developing countries: a major social and economic burden. Annals of Thoracic Medicine, 3 (2): 39-43.
6. **Meyers D, Bleecker E, Holloway *et al.* (2014):** The Genetics of Asthma: Towards a Personalised Approach to Diagnosis and Treatment. Lancet Respir Med., 2 (5): 405–415.
7. **Tost J, Gut I (2007)**: Analysis of gene-specific DNA methylation patterns by pyrosequencing technology. Methods Mol Biol., 373: 89–102.
8. **Kabesch M (2016):** Early origins of asthma (and allergy): Mol Cell Pediatr., 3: 31- 35.
9. **Belsky D, Sears M (2014):** The Potential to Predict the Course of Childhood Asthma. Expert Rev Respir Med., 8: 137- 141.
10. **Lambrecht B, Hammad H (2015):** The immunology of asthma. Nature Immunology, 16 (1): 45- 56.
11. **Morris M, Pearson D, Mosenifar Z (2023):** Asthma Guidelines. Medscape Medical. https://emedicine.medscape.com/article/296301-guidelines
12. **McKenzie A (2014):** Type-2 innate lymphoid cells in asthma and allergy. Ann Am Thorac Soc., 11: 263-270.
13. **Artis D, Spits H (2015):** The biology of innate lymphoid cells. Nature, 517: 293- 301.
14. **Hoppenot D, Malakauskas K, Lavinskiene S *et al.* (2015):** p-STAT6, PU.1, and NF- κB are involved in allergen-induced late-phase airway inflammation in asthma patients. BMC Pulmonary Medicine, 15: 122-133.
15. **Domingo C (2017):** Overlapping Effects of New Monoclonal Antibodies for Severe Asthma. Drugs, 77: 1769-1787.
16. **Rijt L, Richthofen H, Ree R (2016):** Type 2 innate lymphoid cells: at the cross- roads in allergic asthma. Semin Immunopathol., 38: 483- 496.
17. **Parulekara A, Diamant Z, Hanania N (2017):** Role of biologics targeting type 2 airway inflammation in asthma: what have we learned so far? Curr Opin Pulm Med., 23: 3- 11.
18. **Koch S, Sope N, Finotto S (2017):** Th9 and other IL-9-producing cells in allergic asthma. Semin Immunopathol., 39: 55- 68.
19. **Sheharyar R, Durrani Ravi K (2011):** Viswanathan and William W. Busse.What effect does asthma treatment have on airway remodeling? Current perspectives. J Allergy Clin Immunol., 128: 439-48.
20. **Dinarello C, Arend W, Sims J *et al.* (2010):** IL-1 family nomenclature. Nat. Immunol., 11: 973. doi: 10.1038/ni1110-973.
21. **Luo J, An X, Yao Y *et al.* (2019):** Epigenetic regulation of IL-17-induced chemokines in lung epithelial cells. Mediat Inflamm., 19: 9050965. doi: 10.1155/2019/9050965
22. **Lee J, Tato C, Joyce-Shaikh B *et al.* (2015):** Interleukin-23-independent IL-17 production regulates intestinalepithelial permeability. Immunity, 43: 727–738.
23. **Espinoza J, Takami A, Nakata K *et al.* (2011):** A genetic variant in the IL-17 promoter is functionally associated with acute graft-versus-host disease after unrelated bone marrow transplantation. PLoS One, 6: 1–8.
24. **Niu X, Weng X, Zhang H *et al.* (2015):** TERT Polymorphism rs2736100-C Is Associated with EGFR Mutation-Positive Non-Small Cell Lung Cancer. Clin. Cancer Res., 21: 5173–5180.
25. **Wei N, Nograles K, Fuentes-Duculan J *et al.* (2015):** Comparative genomic profiling of synovium versus skin lesions in psoriatic arthritis. Arthritis Rheumatol., 67 (4): 934–44.
26. **Hasegawa T, Uga H, Mori A *et al.* (2017):** Increased serum IL-17A and Th2 cytokine levels in patients with severe uncontrolled asthma. European Cytokine Network, 28 (1): 8–18.
27. **Resendea E, Todo-Bomb A, Loureiro C *et al.* (2016):** Asthma and rhinitis have different genetic profiles for IL13, IL17A and GSTP1 polymorphisms. Rev Port Pneumol., 23: 10-16.
28. **Du J, Han J, Zhang Y *et al.* (2017):** Single-nucleotide polymorphisms of IL-17 gene are associated with asthma susceptibility in an Asian population. Med Sci Monit., 22: 780–787.
29. **Bullens D, Truyen E, Coteur L *et al.* (2006):** IL-17 mRNA in sputum of asthmatic patients: linking T cell-driven inflammation and granulocytic influx? Respir Res., 7: 135. doi: 10.1186/1465-9921-7-135.
30. **Kim H, Lee H, Chang Y *et al.* (2014):** Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. Nat Med., 20: 54–61.
31. **Hinks T, Zhou X, Staples K *et al.* (2015):** Innate and adaptive T cells in asthmatic patients: relationship to severity anddisease mechanisms. J Allergy Clin Immunol., 136: 323–333.
32. **Siew L, Wu S, Ying S *et al.* (2017):** Cigarette smoking increases bronchial mucosal IL-17A expression in asthmatics,which acts in concert with environmental aeroallergens to engender neutrophilic inflammation. Clin Exp Allergy, 47: 740–750.
33. **Lezmi G, Abou Taam R, Dietrich C *et al.* (2018):** Circulating IL-17-producing mucosal-associated invariant T cells (MAIT) are associated with symptoms in children with asthma. Clin Immunol., 188: 7–11.