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Progress on the advanced prevalence and treatment of childhood asthma based on genetic and epigenetics mechanisms

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Abstract. Over the previous ten years, there has been a notable escalation in the global prevalence of asthma in children. This increased incidence has predominantly manifested in regions and countries with greater economic development. Therefore, it demands significant attention. The occurrence of childhood asthma is known to be influenced by both genetics and epigenetics. Epigenetics, e.g., DNA methylation, can be influenced by the environmental factors, thus affect gene expression. These environmental factors include exposure to smoking, viral infections, allergens, and endotoxins. This article analyzes relevant research in recent years and finds that: Regarding genetics, several susceptible genes associated with childhood asthma have been identified, such as ORMDL3, GSDMB, RAD50, HLA-G, CXCR5, IL-4, IL-13 and TSLP; In recent times, it has been observed by an expanding body of researchers that the interplay between environmental elements and genetic factors collectively influence the onset and progression of asthma. Nowadays, the primary treatment for asthma involves medication, while immunotherapy is still under investigation. Therefore, strengthening the prevention of childhood asthma is of utmost importance.

Keywords: Asthma, Genetics, Epigenetics, Prevention, Treatment.

1. Introduction

The prominence of asthma as a major global health concern cannot be overlooked. With a global prevalence ranging from 1% to 18%, the annual rate of increase for this condition is noteworthy. By 2019, around 262 million individuals worldwide were afflicted by asthma, with an estimated 460,000 fatalities attributable to this disease. Asthma in children, in particular, has a higher morbidity and mortality compared to asthma in adults. Around 250 thousand children die prematurely every year because of asthma, unfortunately, plenty of these deaths are preventable. The mortality of asthma in children ranges from 0 to 0.7 per 100,000 people around the world wide. In the United States, over 9 million children have been diagnosed with asthma, 5.5 million children currently have asthma [1].

As delineated by the Global Initiative for Asthma (GINA), asthma constitutes a heterogeneous disease typified by enduring inflammation of the airways. This condition is characterized by a historical record of respiratory distress, including symptoms such as wheezing, episodes of breath shortness, chest constriction, and coughing. These symptoms exhibit variable durations and intensities, often

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accompanied by differing degrees of airflow limitation during exhalation[2].Besides symptoms, it is also combined with asthma experiments: to detect whether the FEV1/FVC ratio < 0.7; FeNO (fractional exhaled nitric oxide testing), measures the amount of nitric oxide in exhaled breath,>25 of parts per billion(ppb)is suspicious of asthma. Whether symptoms can be significantly improved after using bronchodilators, etc.[2]. The precise mechanisms propelling the development of asthma remain to be fully elucidated. Present understanding suggests that environmental and personal behavioral elements may impact epigenetic modifications, thus influencing the expression of genes associated with asthma susceptibility. These epigenetic changes subsequently lead to interactions among airway inflammatory mediators, airway remodeling, airway hyperresponsiveness, abnormal airway smooth muscle structure and function, and imbalanced airway neural regulation, ultimately culminating in the manifestation of asthma.

The aim of this study is to explore the potential for preventing the onset of asthma in children by taking into account genetic factors, familial medical history, and allergens. Currently, the known treatments for asthma are mainly aimed at relieving symptoms. Although it can alleviate and delay the progression of the disease but it cannot provide a cure for the children who already have asthma. In this article, the author believes that keeping in depth research on preventing childhood asthma can lead to more effective treatment outcomes, which holds significant relevance for achieving complete remission in children with asthma.

Within the past three years, there has been no comprehensive review published that discusses the etiology, mechanisms, prevention, and treatment of childhood asthma. Therefore, this review will primarily focus on the genes, family history, and risk factors associated with childhood asthma, combining these factors with the mechanisms, prevention, and treatment of childhood asthma to provide a greater understanding of the condition. This article is based on the genetics and epigenetic analysis using data from Genome-Wide Association Studies (GWAS), epigenome-wide association study (EWAS) and as well as the prevalence and the therapeutics of asthma by the Global Initiative for Asthma (GINA) and asthma-related literatures from 2020-2023.

2. Genetics in childhood asthma

2.1. Classification of genetic factors influencing childhood asthma

Classification of genetic factors influencing childhood asthma: Genetic factors, based on the current findings from GWAS, research has unveiled hundreds of genes linked to asthma susceptibility, scattered across multiple chromosomes. These genes regulate multiple signaling pathways involved in airway hyperresponsiveness, airway remodeling, airway inflammation responses, acute exacerbations, smoking and environmental stimuli, as well as genes related to obesity Environmental factors not only have the potential to influence these genes but there is also an interplay between them at various genetic loci, contributing to the progression of asthma.

The associated genetic factors are presented in Table 1.

These factors can be broadly categorized as follows, with detailed mechanisms discussed in the epigenetics section of this paper:

Genes influencing IgE-mediated airway inflammation and immune responses: ORMDL3, GSDMB, RAD50, IL2, IL5, IL4, IL4R, IL21R, IL-6, IL-9, IL0, IL13, IL1R1, STAT6,

Genes influencing non-IgE-mediated airway inflammation and immune responses: IL-33, IL-1α, IL-1β, TBX21, FAM, TSLP, CXCL-1,CXCR5,CCL20,CCL24.

Genes influencing lung function: ADRB2, TNF-α [3].

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Table 1. A list of childhood asthma-associated genes [4].

Reported Gene(s)	Strongest SNP-risk Allele	Risk Allele Frequency	P-Value	Odd Ratio	95% Confidence Interval
GSDMB, ORMDL3	rs4795399-t	0.529	1E-111	1.406	[1.365-1.448]
STAT5B, STAT5A	rs8066625-A	0.1	5E-9	1.151	[1.098-1.206]
TBX21	rs56308324-T	0.132	3E-9	1.132	[1.086-1.180]
IL1RL1, IL1RL2	rs72823641-T	0.863	3E-46	1.415	[1.349-1.484]
CCL20,	rs10175070-G	0.251	4E-12	1.122	[1.086-1.160]
IL2, IL21	rs2069763-A	0.334	2E-14	1.126	[1.092-1.160]
TSLP	rs1837253-C	0.74	2E-27	1.211	[1.169-1.253]
IL4	rs2051809-A	0.247	3E-22	1.175	[1.137-1.214]
CXCR5	rs12365699-G	0.833	2E-13	1.167	[1.120-1.216]
STAT6	rs3122929-T	0.404	7E-17	1.134	[1.101-1.167]
IL4R, IL21R	rs3785356-T	0.297	6E-13	1.122	[1.087-1.157]
IL6	rs34880821-A	0.283	5E-10	1.106	[1.071-1.141]
IL33	rs992969-A	0.252	7E-42	1.248	[1.209-1.289]
CYP1B1	rs232542-C	0.69	4E-6	1.33	[1.18-1.50]
KLHL1	rs7334050-G	1.69	4E-8	1.58	[1.34-1.86]
NIN	rs7493885-G	2.69	3E-6	1.37	[1.20-1.56]
MACROD2	rs13037508-A	3.69	5E-7	1.48	[1.27-1.72]

2.2. Gene-gene interactions

Researchers have employed Multifactor Dimensionality Reduction (MDR) analysis to investigate gene-gene interactions and have discovered a synergistic effect between IL1RL1 and TLR4 genes in the specific IgE-mediated immune response to indoor allergens [10]. Studying gene-gene interactions contributes to understanding the pathogenic mechanisms of asthma and predicting susceptibility to asthma from a genetic perspective. Given the complexity of gene-gene interactions, future research should utilize systems biology approaches to comprehensively explore gene interaction networks.

3. Epigenetics in childhood asthma

Epigenetics is distinct from genetics as it does not involve changes in DNA sequences but rather affects the expression of genes in various circumstances. Genetics influences gene expression on DNA sequences, thereby determining when and how proteins are expressed. In contrast, Epigenetics involves the examination of how alterations in gene function may be driven by behaviors and environmental factors, without changes to the underlying DNA sequence. This includes processes such as DNA methylation, alteration of microRNA expression and histone modification. These pathways can control the activation or inactivation of genes.

3.1. DNA methylation

Generally, DNA methylation is referred to as “gene silencing,” while DNA demethylation is referred to as “gene activation.” When asthma happens, most time researchers can find the phenomenon of DNA methylation in cells. The process involves adding chemical groups to DNA, typically at specific positions, which can hinder the attachment of proteins to DNA and prevent transcription from occurring. This chemical group can be removed through a process called “demethylation.”

The most frequently investigated variant of DNA methylation within the realm of epigenetic mechanisms is CpG-DNA methylation. In this procedure, a methyl group is integrated into the cytosine

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of a CpG dinucleotide, hence transforming cytosine into 5'-methylcytosine. This modification at the genetic locus results in an inability to transcribe into RNA and culminates in gene non-expression [5]. Four loci have been identified, with high methylation in eosinophilic asthma, paucigranulocytic asthma, neutrophilic asthma, and CD4 $^{+}$ T cells, suggesting these four cell types: eosinophils, granulocytes, neutrophils and CD4^{+}T cells have significant associations with childhood asthma.

Allergen sensitization leads to hypermethylation of the IFN-y loci in CD4 + T cells. In eosinophils asthma, three pathways have been identified, including calcium signaling, ECM (The extracellular matrix)-receptor interaction and purine metabolism. In the case of paucigranulocytic asthma, two confirmed pathways exist. These include the pathway involving neuroactive ligand-receptor interaction and the pathway involving ubiquitin-mediated proteolysis. Simultaneously, the DNA loci of two cytokines secreted by macrophages, TBX521 and FAM, demonstrate high methylation. In neutrophilic asthma, a network with sFRP1 as a central locus signifies the Wnt signaling pathway [6].

3.2. Histone Modification

Histone modification is the process wherein core histones package DNA into a structure called chromatin. The core histones are differentiated to H2, H3, and H4. Histone modifications include methylation, acetylation, etc. [5].

3.3. Expression of microRNA (miRNA)

Studies show that some miRNAs in asthmatic children are significantly upregulated.

miR-21 and miR-126 are upregulated in asthmatic patients, with miR-21 promoting the production and proliferation of eosinophilic granulocytes, while miR-223 inhibits the same process.

miRNA-9 can polarize macrophages towards the M1 phenotype (M1 macrophages produce cytokines and transcription factors like NF-kB, TNF-α, IFN-γ, IL-1, IL-6, IL-12, IL-23 during acute inflammation). In severe asthmatic children, miRNA-9 expression is upregulated in epithelial cells, targets TGFB2 mRNA, this mRNA's function is to code TGF-β, forming the TGF-β/SMAD pathway. miRNA-9 inhibits TGFB2 mRNA, thereby disrupting the formation of this pathway, the result is promoting airway remodeling. The current hypothesis is that the disruption of the TGF-β/SMAD pathway leads to airway remodeling.

Studies have indicated that an increase in miR-21 expression is associated with the differentiation of Th2 cells. miR-27 and miR-128 cause a decrease in IL-4 and IL-5 secreted by Th2 cells.

In conclusion, miRNA-21 is the most extensively studied miRNA in asthma. In experiments, its high expression is associated with the insensitivity to corticosteroids exhibited by asthmatic children during treatment, so it is speculated that it can serve as a biomarker for monitoring asthma experiments in the future [5].

4. The immunology of childhood asthma

Although the immunologic mechanisms of asthma remain unclear, many research studies have made new findings on this exploration path. Figure 1 simply illustrates the currently understood immunological process of asthma in the form of a flow chart. Based on cells and cytokines, it briefly elaborates on the roles of various cells and cytokines in the immune process.

4.1. Eosinophils play many roles in asthma

Eosinophils also have the ability to release various cytokines, like IL4, IL-6 which in turn boosts the production of inflammatory mediators. (Cysteinyl leukotrienes); They can promote airway epithelial cells to secrete cytokines: IL-1α, IL-1β, IL-33, TSLP, CCL24 and Chemokine ligand 1 (CXCL-1) which are very vital in the occurrence of asthma [7]. Extracellular Traps (EETs) are net-like structures made up of DNA, histones, and granular proteins, which are secreted and released by eosinophils into the extracellular environment. EETs serve as part of the innate immune response, affording immune protection to the organism by trapping pathogens within a certain range and restricting their bacterial activity. However, chronic inflammation (persistent, caused by indigestible pathogens, viral infections,

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foreign bodies, or autoimmunity) can lead to excessive production of EETs, thereby triggering and exacerbating asthma [5].

4.2. Macrophages

Macrophages produce TGF-β, FAM, IL-12, and also secrete Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF). GM-CSF can recruit and activate mast cells, eosinophils, Type 2 Innate Lymphoid Cells (ILC2), dendritic cells (DC), and other immune cells. Macrophages influence DCs, which in turn promotes the differentiation of $CD4^+$ T cells into Th2 cells.

4.3. T cells

$CD4^+$ T cells divide into Th1 cells and Th2 cells. Th1 cells release IL-2, TNF-α, and IFN-γ, which lead to the accumulation of macrophages. In response to IL-2, Th2 cells produce cytokines like IL-4, IL-5, IL-10, and IL-13. When exposed to asthma-specific antigens, they induce B cells to differentiate into plasma cells.

4.4. ILCs

Innate lymphoid cells (ILCs), also recognized as innate immune cells, are a recently identified subclass of lymphocytes. They fill the previously known gap in the early stages of the immune response. Within hours of infection, ILCs participate in the immune response to protect the organism while maintaining mucosal integrity and promoting lymphoid organ formation. ILCs are divided into ILC1, ILC2, and ILC3, each participating in the onset of Type 1, 2, 3 immune responses, respectively. ILC2 is responsible for regulating inflammation and immunity in tissues, secreting GATA3, IL-5, IL-13.

4.5. Cytokines

Transforming Growth Factor-beta (TGF-β), which is produced by macrophages and fibroblasts, is the primary mediator. IL-4 promotes Th2 responses, inhibits Th1 responses, activates cells that produce ASM (Acid Sphingomyelinase, also known as SMPD1), leading to increased synthesis of actin and collagen in the airways, thereby promoting airway remodeling. IL-5 promotes the activation of eosinophils. IL-12 promotes and maintains Th1 differentiation. IL-13 promote airway goblet cell metaplasia, therefore promoting mucus secretion and airway remodeling. STAT6 exists in bronchial epithelial cells and goblet cells. IL-13 can activate STAT6, promote TH2 immune response and B cell differentiation, promote goblet cell metaplasia and increase mucus secretion. Research suggests that the Brg1 gene may potentially influence the high secretion of asthma mucus by affecting the STAT6 signaling pathway. IL-33 activates ILC2s, which in turn induces the production of IL-5 and IL-13. These actions lead to the release of collagen and fibronectin from airway fibroblasts, contributing to the structural changes in the airway walls. IgE: stimulates the production of leukocyte interleukins, such as IL-4, binds with mast cells, basophils, and DCs to induce these cells to produce cytokines.

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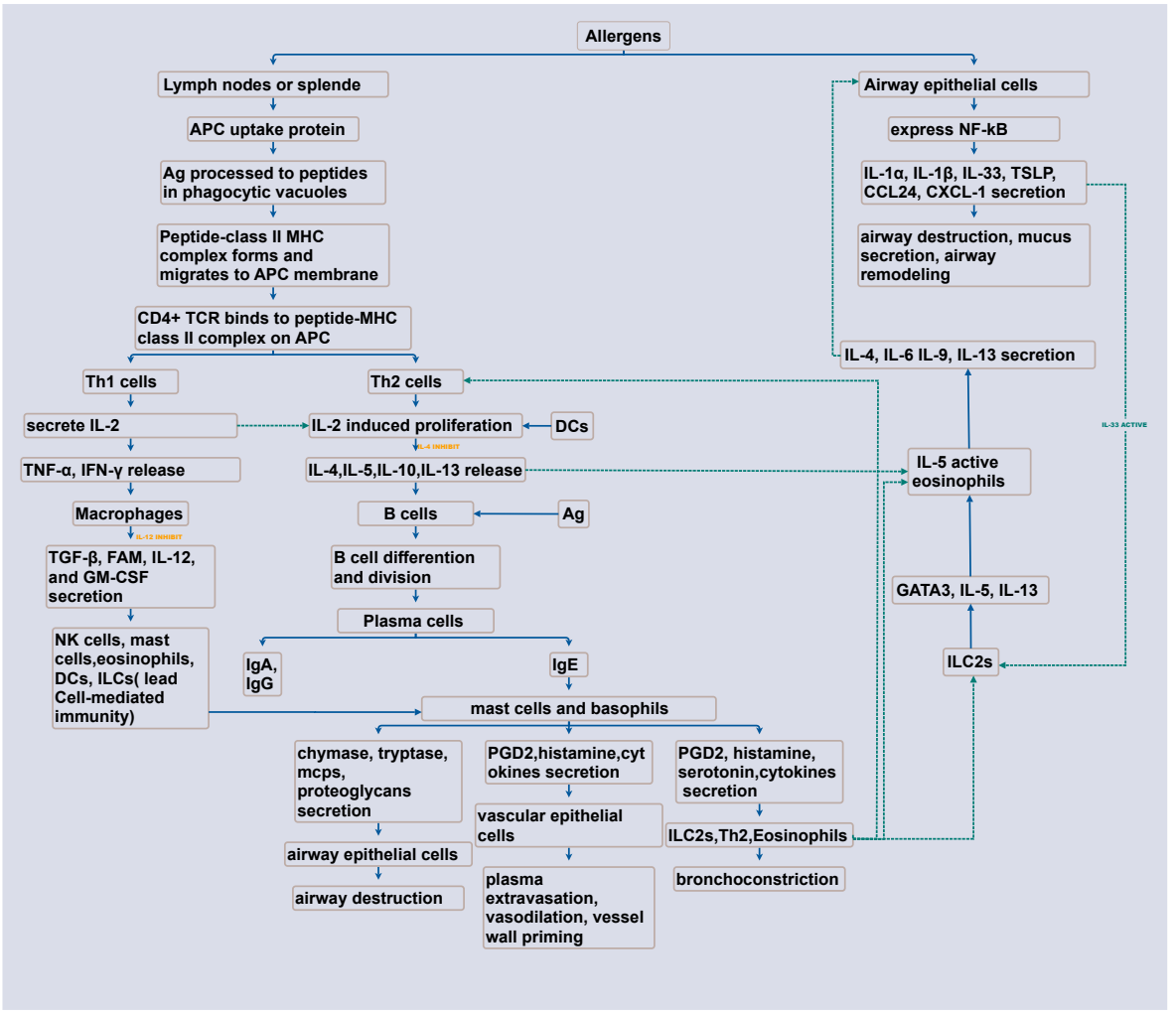

Figure 1. Immune mechanism of asthma [8].

5. Influence of environmental and behavioral factors on genetics

When children with asthma-susceptible genes are exposed to environmental factors, these factors can induce the expression or silencing of one or more asthma-related alleles, without causing DNA sequence mutations. Accordingly, environmental determinants contribute to the modulation of genetic transcription, thereby affecting the initiation of asthma and amplifying the predisposition towards contracting this condition, a process denominated as epigenetic alteration. This shows that genetic and environmental factors interact to cause asthma, implying that the disease is not the result of a single factor. This concept, first proposed by Waddington, his elucidates the intricate association between environmental influences and genetic determinants in relation to asthma, thereby paving the way for novel research trajectories concerning the etiology of asthma [3].

5.1. Risk factors

The onset and progression of asthma in children are influenced by a range of factors during both the maternal pregnancy and childhood period.

During the maternal pregnancy period, factors such as maternal smoking, inappropriate diet, stress, use of antibiotics can influence the development of asthma.

In childhood, tobacco smoke-exposed - which has been shown to have associated with genes such as KLHL1, MACROD2, NIN, PYGL, and CYP1B1 [4], inappropriate diet (like fatty diet), obesity, intake too much dairy products, lack of some nutrition, e.g. Vitamin C, D, E, β-Carotene, polyunsaturated fatty

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acids, antioxidants, fibers [9]; exposure to pets, air quality(considered it has connected with Th2 and Th17 cells) , gastrointestinal and respiratory microbiome (like, induce the generate of T cells)and antibiotic use, as well as eczema and gender, can further affect asthma progression [10, 11].

Other potential factors remain unclear due to ongoing research and conflicting study results, preventing a definitive conclusion from being drawn at this point. However, it can be postulated that certain factors, such as viral lower respiratory infections and family size and structure, may be related to asthma development and progression [1].

5.2. Protective factor

Multiple studies have shown that children with asthma risk alleles such as chromosome 17q21 have a greatly reduced incidence of asthma when they grow up on traditional European and American farms, possibly due to long-term high exposure to various bacteria, viruses, dust and other factors, while also eating unprocessed milk, resulting in increased immunity. Therefore, the farm environment currently appears to be asthma-friendly [12].

6. Treatments

6.1. Current classical clinical pharmacological treatments

For mind asthma, daily medication is not necessary. Nonetheless, the utilization of short-acting β2-agonists (SABA) exceedingly twice per week might indicate the necessity of commencing long-term regulatory treatment. In cases of mild persistent asthma, the daily administration of a long-term control treatment (such as inhaled corticosteroids, ICS) becomes imperative. For moderate persistent asthma, the application of ICS is obligatory, either in isolation or conjoined with additional long-term regulatory medications. In instances of severe persistent asthma, multiple long-term control medications, including high-dose inhaled corticosteroids, and potentially, oral corticosteroids, become necessary.

However, one study, 101 777 children, the inclusion of 63 centers across 25 nations demonstrates that a significant proportion of pediatric asthma patients globally used short-acting beta2-agonists and inhaled corticosteroids ICS, only 44% of children had better disease control [13].

6.2. Immunotherapy

6.2.1. Allergen immunotherapy. Allergen immunotherapy (AIT), via sublingual (SLIT) or subcutaneous (SCIT)pathways, represents a novel therapeutic approach for asthma management, employing anti-IgE, IL-4, and other targeted antibodies [14]. The mechanism of AIT is shown in figure 2.

Anti-IgE: Omalizumab exemplifies a humanized IgG1-κ monoclonal antibody (mAb). The procedure of antibody humanization involves genetic modification to transfer human antibody genes to genetically modified animals, such as mice, that lack specific antibody genes, enabling these animals to express human antibodies. Moreover, since these humanized antibodies have an extremely similar profile to the original antibodies in the human body, they can evade recognition by the human immune system and function similarly within it. This has significant implications for the clinical application of antibodies in targeted therapy. Omalizumab attaches to the Fc fragment of IgE, thus inhibiting the high affinity of IgE for mast cells, basophils, and DCs in humans.

Anti-IL-5/IL-5R: Mepolizumab, Reslizumab, and Benralizumab are humanized IgG1-κ mAbs that target and bind to the Fc fragment of IL-5Rα on eosinophils. They then induce natural apoptosis of eosinophils by activating the cytotoxicity of NK cells, macrophages, and neutrophils.

Anti-IL-4/IL-4R, Anti-IL-13/IL-13R: Dupilumab is a humanized IgG4 monoclonal antibody that specifically targets and binds to IL-4Rα and IL-13α on lymphocytes.

Anti-TSLP: Tezepelumab is a humanized IgG2-γ mAb with high affinity for TSLP (figure 2) [14].

Other Unclear Antibodies: Such as Anti-IL-33/IL-33R, Astegolimab [15].

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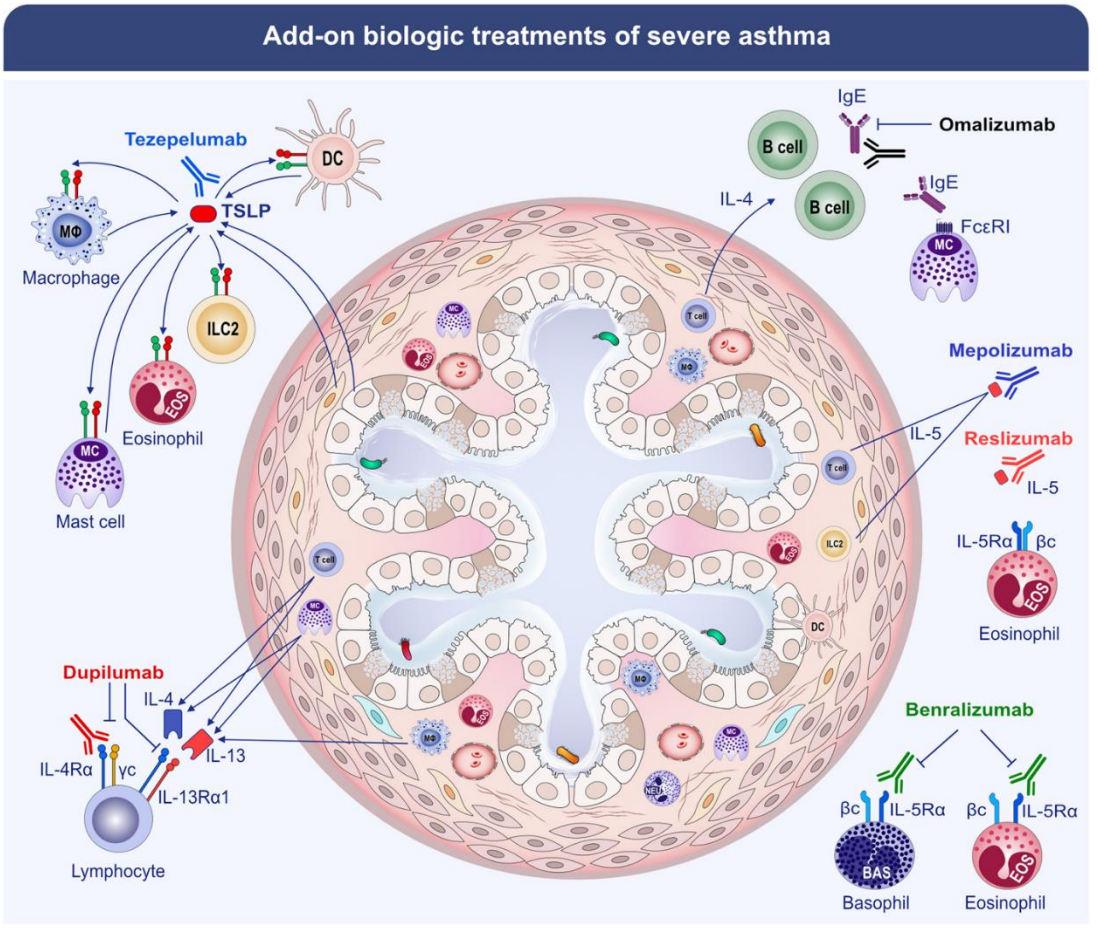

Figure 2. The mechanism of biologic anti-body treatment [14].

6.2.2. Acupuncture Emerging treatments. Acupuncture shows promise in promoting changes in biomarkers, potentially due to TSG-12, an inhaled transgelin-2 agonist. TSG12 has been shown to decrease airway hyperresponsiveness, effectively alleviating asthma, hence acupuncture may be used in the treatment of asthma [16].

6.3. Biological and Airway Remodeling Therapies

Airway remodeling can affect the trachea, bronchi, and bronchioles. There are ECM (Collagen fibers, fibronectin, and tenascin) deposition on the propria and reticular basement membrane (RBM) as well as in the submucosa, is distinctive of asthma. Evidence suggests that certain biologicals can not only improve clinical symptoms but also improve FEV1 and FEV1/FVC, such as the HSP90 inhibitor, geldanamycin, can mitigate airway goblet cell metaplasia caused by IL-13 [17].

6.4. Bronchial Thermoplasty

Bronchial Thermoplasty (BT) is a unique therapy that uses controlled thermal energy to reduce the amount of excessive smooth muscle in the airway. This lessens the muscle's ability to constrict the airways, thus decreasing the frequency and severity of asthma attacks. It is typically offered to patients with severe persistent asthma that is not well-controlled by inhaled corticosteroids and long-acting beta-agonists. This can improve quality of life by reducing asthma symptoms and exacerbations [16].

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7. Prevention

Considering the growing importance of environmental factors in asthma, preventive education should be strengthened as soon as possible.

7.1. Environment factors prevention

Guardians of children with asthma need to be taught to create an environment conducive to the child's growth, which includes maintaining cleanliness at home, staying away from smoky places, avoiding known or common allergens such as dust, pollen, hair, certain plants, avoiding cold air stimulation, reducing unnecessary antibiotic use, etc.

7.2. Nutrition prevention

Indeed, a diet high in fruits and vegetables has been found to potentially reduce the risk of asthma in children. In addition to this, a case-control study conducted in 2015 compared children with different levels of dairy intake. The results showed a negative correlation between dairy intake and asthma control. The more dairy children consume, the higher the risk of asthma. However, current Western dietary guidelines recommend three cups of dairy per day. The author suggests reducing the daily intake of dairy for asthmatic children. The current Western diet fails to meet the daily recommended intake of fruits or vegetables for children with asthma and exceeds the recommended limit for saturated fats. Therefore, the author suggests that children with asthma adopt healthy eating habits, such as trying the Mediterranean diet, eating natural foods, green vegetables, superfoods, etc., which can lower the risk of asthma. The risk of wheezing observed in preschool children may be mitigated by the intake of elevated levels of vitamin D or fish oil during gestation [9].

8. Conclusion

In conclusion, environmental and behavioral factors, such as diet and exercise, can result in epigenetic changes that interplay between genes, behaviors, and the environment. Hence, it is broadly accepted that a pivotal role in the pathogenesis of asthma is played by epigenetics, however, it is crucial to note that results may vary, and more extensive research is required to firm up the conclusions. Similarly, the current immunotherapies and preventive measures for asthma are still under active research, with few examples put into clinical use, thus limiting the discussion of this paper. It is the aspiration of the author that forthcoming investigations persist in elucidating the function of both epigenetics and genetics within immunological responses, in addition to focusing on preventative measures and therapeutic approaches predicated on these immune responses.

References

[1] J. Stern, J. Pier, and A. A. Litonjua, 'Asthma epidemiology and risk factors', Seminars in Immunopathology, vol. 42, no. 1. Springer, pp. 5–15, Feb. 01, 2020

[2] Global Initiative for Asthma and GINA, 'Pocket guide for asthma management and prevention 2023', GINA.

[3] P. Ntontsi, A. Photiades, E. Zervas, G. Xanthou, and K. Samitas, 'Genetics and epigenetics in asthma', International Journal of Molecular Sciences, vol. 22, no. 5. MDPI AG, pp. 1–14, Mar. 01, 2021

[4] GWAS, 'childhood onset asthma '.

[5] P. Ntontsi, A. Photiades, E. Zervas, G. Xanthou, and K. Samitas, 'Genetics and epigenetics in asthma', International Journal of Molecular Sciences, vol. 22, no. 5. MDPI AG, pp. 1–14, Mar. 01, 2021

[6] L. P. Gunawardhana, P. G. Gibson, J. L. Simpson, M. C. Benton, R. A. Lea, and K. J. Baines, 'Characteristic DNA methylation profiles in peripheral blood monocytes are associated with inflammatory phenotypes of asthma', Epigenetics, vol. 9, no. 9, pp. 1302–1316, 2014

[7] G. Van Hulst, H. M. Batugedara, J. Jorssen, R. Louis, F. Bureau, and C. J. Desmet, 'Eosinophil diversity in asthma', Biochemical Pharmacology, vol. 179. Elsevier Inc., Sep. 01, 2020

DOI: 10.54254/2753-8818/17/20240695

[8] H. Hammad and B. N. Lambrecht, 'The basic immunology of asthma', Cell, vol. 184, no. 6. Elsevier B.V., pp. 1469–1485, Mar. 18, 2021
[9] J. Alwarith et al., 'The role of nutrition in asthma prevention and treatment', Nutr Rev, vol. 78, no. 11, pp. 928–938, Nov. 2020
[10] chenjing X Analysis of Influencing Factors of Asthma in Children', Advances in Clinical Medicine, vol. 12, no. 12, pp. 12047–12053, 2022
[11] S. N. Baxi and W. Phipatanakul, 'The Role of Allergen Exposure and Avoidance in Asthma'.
[12] G. D'Amato, O. P. M. Ortega, I. Annesi-Maesano, and M. D'Amato, 'Prevention of Allergic Asthma with Allergen Avoidance Measures and the Role of Exposome', Current Allergy and Asthma Reports, vol. 20, no. 3. Springer, Mar. 01, 2020
[13] L. García-Marcos et al., 'Asthma management and control in children, adolescents, and adults in 25 countries: a Global Asthma Network Phase I cross-sectional study', Lancet Glob Health, vol. 11, no. 2, pp. e218–e228, Feb. 2023
[14] 'Allergen immunotherapy for asthma prevention_ A systematic review and meta-analysis of randomized and non-randomized controlled studies'.
[15] K. Shen et al., 'Eosinophil extracellular traps in asthma: implications for pathogenesis and therapy', Respiratory research, vol. 24, no. 1. NLM (Medline), p. 231, Dec. 01, 2023. doi: 10.1186/s12931-023-02504-4.
[16] X. Lv et al., 'Trends of therapy in the treatment of asthma', Therapeutic Advances in Respiratory Disease, vol. 17. SAGE Publications Ltd, Jan. 01, 2023. doi: 10.1177/17534666231155748.
[17] G. Varricchi et al., 'Biologics and airway remodeling in severe asthma', Allergy: European Journal of Allergy and Clinical Immunology, vol. 77, no. 12. John Wiley and Sons Inc, pp. 3538–3552, Dec. 01, 2022. doi: 10.1111/all.15473.