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ETIOLOGY AND PATHOGENESIS OF BRONCHIAL ASTHMA

Mamadjanov Rustam Ergashevich

Fergana medical institute of public health

Abstarct: This section briefly outlines the etiology and pathogenesis of bronchial asthma. It describes the main causal factors, including genetic predisposition, environmental triggers, and immune system dysfunction. The pathogenesis highlights the chronic inflammatory nature of the disease, airway hyperresponsiveness, and remodeling processes that contribute to symptom development.

Keywords: bronchial asthma, etiology, pathogenesis, inflammation, immune response, airway remodeling.

Bronchial asthma is a multifactorial, chronic inflammatory disease of the airways characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These symptoms are associated with variable and often reversible airflow obstruction and bronchial hyperresponsiveness. While asthma is often viewed through the lens of its clinical manifestations, a comprehensive understanding of its underlying causes and pathogenesis is essential for effective disease management and the development of individualized treatment plans.

Asthma does not arise from a single cause but rather from the interaction of a range of genetic, environmental, immunological, and lifestyle factors. These components collectively shape the natural history and expression of the disease, and their influence may vary depending on age, exposure, geographical region, and comorbidities.

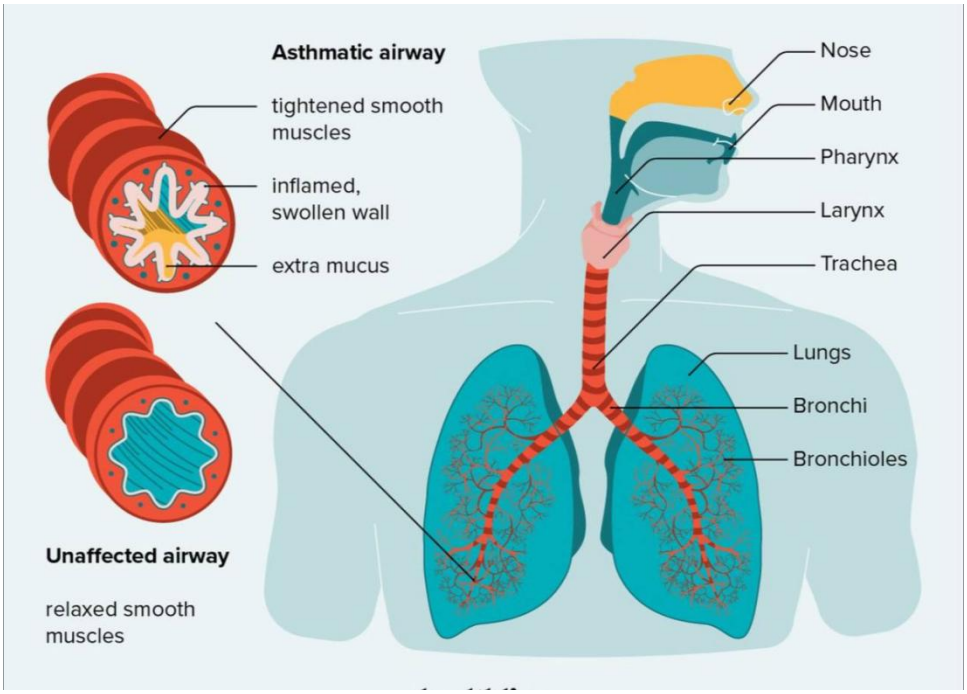

Figure 1.1 Asthmatic vs normal airway anatomy

A comprehensive understanding of bronchial asthma requires consideration of both its etiological diversity and underlying pathophysiological mechanisms. Over the past decades, a significant body of research has been contributed by leading scholars who have shaped contemporary approaches to the classification, diagnosis, and management of asthma as a multifaceted chronic disease.

One of the foremost authorities on asthma pathophysiology is Stephen T. Holgate, who has long argued that asthma should be viewed not merely as an episodic bronchospastic disorder, but as a genetically complex, environmentally modulated condition. His work identified genetic polymorphisms, such as in the ORMDL3 and ADAM33 genes, which play key roles in airway inflammation and remodeling. Holgate also emphasized the interaction between environmental exposures-particularly respiratory viruses and allergens-and genetic predisposition, framing asthma as a product of gene-environment interplay.

Another major contributor to asthma epidemiology is Erika von Mutius, whose studies in Germany compared asthma prevalence between children in East and West Germany following reunification. Her findings supported the "hygiene hypothesis," which posits that reduced microbial exposure in early childhood may skew immune system development toward allergic sensitization. She concluded that children raised in more sterile environments are at greater risk for asthma, especially in the presence of familial atopy.

From the pediatric perspective, Fernando Martinez has provided key insights into early-life determinants of asthma. Through the Tucson Children's Respiratory Study, he demonstrated that early viral respiratory infections, such as those caused by rhinovirus or RSV, significantly increase the likelihood of persistent wheezing and asthma later in life.He also explored how genetic and environmental interactions during critical windows of lung and immune system development can shape long-term respiratory health.

In the domain of immunopathology, Peter J. Barnes has offered a robust framework for understanding the Th2-mediated inflammatory cascade in asthma. His research outlines how interleukins-particularly IL-4, IL-5, and IL-13-coordinate the immune response leading to eosinophilic inflammation, IgE production, and mucus hypersecretion. Barnes also identified key mechanisms by which corticosteroids regulate airway inflammation and described pathways of steroid resistance in severe asthma phenotypes.

A complementary clinical perspective is offered by Sally Wenzel, who contributed to the classification of asthma phenotypes and endotypes based on airway tissue sampling. Her research emphasizes that asthma is not a singular entity, but rather a collection of biologically distinct disorders unified by common symptoms. Wenzel's work highlights the existence of non-eosinophilic, neutrophilic asthma and underscores the importance of tissue biomarkers in guiding precision therapy.

The immunological complexity of severe, steroid-resistant asthma has also been explored by Kian Fan Chung, who investigated the role of **Th17 cells** and the cytokine **IL-17** in promoting neutrophilic inflammation. His work revealed that these pathways are largely unresponsive to corticosteroids, necessitating alternative therapeutic targets for this subgroup of patients.

In terms of therapeutic innovation, Bruce Bochner's research into IgE-mediated pathways has been instrumental in the development of monoclonal antibody treatments such as omalizumab. By targeting circulating IgE and its receptors on mast cells, Bochner demonstrated how the allergic cascade in atopic asthma could be effectively disrupted, offering relief to patients with

moderate-to-severe disease.

Collectively, these scholars have transformed the conceptual landscape of asthma from a simplistic model of bronchial hyperreactivity to a dynamic, systems-level disorder involving epithelial dysfunction, immune dysregulation, environmental provocation, and neuroimmune interaction. Their findings continue to shape global asthma guidelines and underpin the development of phenotype-specific interventions in modern respiratory medicine.

Etiology

Asthma has long been recognized as a disease with both hereditary and environmental roots. The genetic predisposition to asthma is strongly supported by epidemiological studies. Individuals with one or more first-degree relatives who have asthma are significantly more likely to develop the disease. Twin studies have demonstrated that monozygotic twins show greater concordance rates for asthma than dizygotic twins, underscoring a genetic basis.

Several genes implicated in immune regulation and airway physiology have been linked to asthma susceptibility. Polymorphisms in genes encoding interleukins (such as IL-4, IL-5, and IL-13), the high-affinity IgE receptor, and the beta-2 adrenergic receptor have been identified in patients with asthma. Additionally, genome-wide association studies (GWAS) have highlighted genes such as ORMDL3, GSDMB, and ADAM33 as contributors to airway inflammation and remodeling. These genetic variants influence immune responses, mucosal barrier function, airway structure, and responses to environmental triggers.

However, genetic predisposition alone is insufficient to explain the development of asthma. Environmental exposures play a central role in both the initiation and progression of the disease. Common environmental triggers include:

- Aeroallergens such as pollen, dust mites, pet dander, mold spores, and cockroach antigens, which are especially relevant in allergic asthma;
- Air pollution, including fine particulate matter (PM2.5), ozone (O_3), and nitrogen dioxide (NO_2), which exacerbate airway inflammation;
- Tobacco smoke, both direct and second-hand, which is a well-established risk factor for asthma onset in children and adults;
- Respiratory infections, particularly in early childhood, which may alter the normal development of the immune system and epithelial barrier, increasing asthma risk;
- Occupational exposures to chemicals, organic dusts, and industrial irritants that can lead to adult-onset asthma.

Other etiological factors include obesity, dietary patterns, psychosocial stress, low birth weight, and early antibiotic use, all of which may modify immune development and contribute to asthma pathophysiology.

Pathogenesis

The pathogenesis of bronchial asthma is fundamentally rooted in chronic inflammation of the airway mucosa. This inflammatory response is orchestrated by a complex network of immune cells, cytokines, chemokines, and structural elements of the airway. While the specific mechanisms may differ between phenotypes (e.g., allergic vs. non-allergic asthma), several key features are consistently observed.

One of the defining immunological mechanisms in asthma is the dominance of type 2 helper T-cell (Th2) responses. Upon exposure to allergens, antigen-presenting cells process and present antigens to naïve T cells, promoting their differentiation into Th2 cells. These Th2 cells secrete interleukins IL-4, IL-5, and IL-13. IL-4 stimulates B cells to produce immunoglobulin E (IgE),

which binds to the surface of mast cells and basophils. IL-5 promotes eosinophil maturation, activation, and survival. IL-13 contributes to goblet cell hyperplasia, mucus hypersecretion, and airway hyperreactivity.

Mast cells, once sensitized by allergen-specific IgE, undergo degranulation upon subsequent allergen exposure. This leads to the rapid release of histamine, leukotrienes, prostaglandins, and platelet-activating factors-potent mediators that initiate bronchoconstriction, vascular leakage, and recruitment of additional inflammatory cells. The early-phase allergic response may be followed by a late-phase reaction, characterized by sustained inflammation and tissue remodeling.

Eosinophils play a central role in perpetuating airway inflammation. They release cytotoxic granules containing major basic protein and eosinophil cationic protein, which damage epithelial cells and expose underlying nerves, leading to increased bronchial sensitivity. Their presence in sputum and bronchial biopsy specimens is a hallmark of eosinophilic asthma, which is often associated with better responsiveness to corticosteroids.

In non-eosinophilic asthma, other inflammatory cells such as neutrophils, Th17 cells, and innate lymphoid cells (ILCs) dominate. This phenotype is frequently observed in adult-onset, obese, or corticosteroid-resistant patients and may represent a distinct pathophysiological subtype.

Airway hyperresponsiveness is another key feature of asthma pathogenesis. It reflects an exaggerated constrictive response of the airway smooth muscle to various nonspecific stimuli, such as cold air, exercise, or irritants. This phenomenon is thought to result from a combination of inflammation, epithelial damage, altered neural regulation, and structural changes in the airway wall.

Chronic inflammation in asthma is associated with airway remodeling, a process characterized by persistent structural changes that may lead to irreversible airflow limitation. Histological findings include thickening of the reticular basement membrane, increased smooth muscle mass, goblet cell and submucosal gland hyperplasia, angiogenesis, and fibrosis. These changes may occur early in the disease course and are thought to contribute to the progressive nature of severe asthma.

Moreover, neural mechanisms contribute to asthma symptoms. Inflammation-induced injury to airway sensory nerves increases their excitability, leading to reflex bronchoconstriction and cough. There is also evidence of increased parasympathetic tone in asthmatic individuals, resulting in heightened acetylcholine-mediated bronchial constriction.

Asthma is now recognized not as a single disease, but as a syndrome encompassing multiple phenotypes and endotypes. Phenotypes refer to observable characteristics (e.g., allergic, late-onset, exercise-induced), whereas endotypes reflect the underlying biological mechanisms. This understanding has spurred interest in precision medicine, with treatments increasingly tailored to the specific inflammatory profile of the patient-such as the use of anti-IL-5 or anti-IgE monoclonal antibodies in severe eosinophilic asthma.

Recent advancements in immunology and cellular biology have deepened our understanding of bronchial asthma, revealing that its pathogenesis extends well beyond the classical Th2-mediated inflammatory model. While type 2 immunity remains a central mechanism, especially in allergic asthma, newer research highlights the heterogeneity of immune responses and the involvement of multiple cellular and molecular pathways.

A notable development is the recognition of epithelial cell dysfunction as a key early event in asthma pathogenesis. The airway epithelium is no longer viewed merely as a passive barrier but as an active immunological participant. In response to inhaled allergens, pollutants, or viruses,

epithelial cells release **alarmins**—notably **IL-25**, **IL-33**, and thymic stromal lymphopoietin **(TSLP)**. These cytokines activate innate lymphoid cells (ILC2s) and amplify type 2 inflammation even in the absence of adaptive immune cells. This is especially relevant in children, where early epithelial-immune interactions may shape disease susceptibility.

Moreover, the concept of epigenetic modulation has gained attention. Environmental exposures such as tobacco smoke or pollutants can induce epigenetic changes-such as DNA methylation, histone modification, and microRNA expression-that alter gene expression related to inflammation, immune regulation, and tissue remodeling. These heritable yet reversible changes may explain why genetically similar individuals experience differing disease courses.

Another critical dimension of asthma pathogenesis is oxidative stress. Inflammatory cells such as eosinophils and neutrophils generate reactive oxygen species (ROS), which further damage the epithelium, stimulate mucus production, and impair β_2-adrenergic receptor function. Oxidative stress is particularly elevated in obese individuals and those with severe, steroid-resistant asthma, making it a potential target for antioxidant-based therapy.

In recent years, the gut–lung axis has emerged as an area of interest in chronic respiratory diseases. Dysbiosis, or an imbalance in gut microbiota, has been shown to influence systemic immune responses and promote allergic sensitization. Short-chain fatty acids (SCFAs), produced by commensal bacteria, have immunomodulatory effects, and a deficiency in SCFAs may predispose individuals to heightened Th2 responses. Similarly, alterations in the airway microbiome may directly impact the severity and phenotype of asthma.

From a structural standpoint, increasing attention is being paid to the role of airway smooth muscle (ASM) cells. Beyond their contractile function, ASM cells can secrete cytokines, express pattern recognition receptors, and interact with immune cells, contributing to both inflammation and remodeling. Their proliferation and phenotypic shift into a more secretory state are believed to sustain chronic disease progression and reduce bronchodilator responsiveness.

The neuroimmune interface is another underexplored contributor to asthma pathogenesis. Neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are upregulated in asthmatic airways and can increase sensory nerve density, enhance reflex bronchoconstriction, and even promote mast cell survival. These factors may help explain the heightened cough reflex and airway irritability seen in certain phenotypes.

In severe asthma, especially corticosteroid-resistant variants, non-Type 2 pathways involving **Th1** and **Th17** cells dominate. These pathways are associated with neutrophilic inflammation, increased production of **IL-17**, and reduced response to conventional inhaled corticosteroids. The development of biologics targeting these non-eosinophilic pathways is a current area of clinical research.

Finally, metabolic dysregulation and systemic inflammation, particularly in obese asthmatics, represent an important pathogenic axis. Adipose tissue–derived cytokines like leptin, adiponectin, and resistin modulate lung inflammation and immunity. This phenotype often presents with lower eosinophilic inflammation but more severe symptoms and poor treatment response.

The etiology and pathogenesis of bronchial asthma are deeply complex, involving a multifaceted interaction between genes, environment, immunity, and airway structure. While the manifestations of asthma may be similar across patients, the underlying mechanisms can vary greatly, necessitating individualized approaches to diagnosis and treatment. Continued research into the molecular and cellular pathways of asthma pathogenesis is essential for the development of novel therapies and for improving outcomes in patients with difficult-to-treat or severe asthma.

References

1. Holgate, S. T. (2008). Pathogenesis of asthma. *Clinical & Experimental Allergy, 38*(6), 872–897. https://doi.org/10.1111/j.1365-2222.2008.03071.x

2. Martinez, F. D. (2009). The origins of asthma and chronic obstructive pulmonary disease in early life. *Proceedings of the American Thoracic Society, 6*(3), 272–277. https://doi.org/10.1513/pats.200808-090RM

3. Bateman, E. D., Bousquet, J., Keech, M. L., Busse, W. W., Clark, T. J. H., Pedersen, S. E., & Thompson, P. J. (2008). Overall asthma control: The relationship between current control and future risk. *Journal of Allergy and Clinical Immunology, 125*(3), 600–608. https://doi.org/10.1016/j.jaci.2009.10.007

4. Bousquet, J., Anto, J. M., Bachert, C., et al. (2010). Prevention of asthma: What are the possibilities? *European Respiratory Journal, 36*(5), 1172–1187. https://doi.org/10.1183/09031936.00053710