Asthma: a new approach to the bronchial epithelium

ASTMA: NAUJAS POŽIŪRIS Į BRONCHŲ EPITELĮ

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Summary. The bronchial epithelium serves as a critical defense line against environmental insults, acting not merely as a barrier but as a complex, dynamic system enriched with diverse cell types such as ciliated cells, goblet cells, and basal cells. Recent advancements in single-cell ribonucleic acid (RNA) sequencing have further unveiled the complexity of this layer by identifying additional cell types like ionocytes, neuroendocrine cells, tuft cells, deuterosomal cells, club cells and mucus ciliated cells. These cells collectively maintain respiratory health through various mechanisms including the mucociliary escalator, mucus production, airway repair, and immune modulation. Disruptions in the epithelial barrier can lead to respiratory diseases like asthma, highlighting the importance of understanding these intricate cellular relationships for developing targeted therapies. This epithelial complexity is crucial for pulmonary homeostasis and the pathogenesis of asthma, where abnormal epithelial remodeling and dysfunction are central. The identification of a novel mucous ciliated cell state in asthma, co-expressing genes associated with both ciliated and goblet cells, offers new insights into the disease's pathogenesis and therapeutic targets. The epithelial barrier's integrity, maintained by tight junctions and adherents' junctions, is essential for protecting the underlying tissue from environmental threats. However, in asthma, this barrier is compromised, leading to increased allergen permeability, airway hyperresponsiveness, inflammation, and remodeling. Despite advances, the need for novel concepts in asthma pathogenesis remains, particularly to address the limitations of the current T helper 2-dominant paradigm in explaining the connection between airway inflammation and remodeling. Understanding the molecular mechanisms underlying epithelial barrier dysfunction could pave the way for novel asthma treatments focused on enhancing barrier integrity, ultimately improving patient outcomes.
Keywords: epithelium, asthma, structural cells, barrier dysfunction, airway remodeling.
Santrauka. Bronchų epitelis yra kritinė gynybos linija prieš aplinkos veiksnius bei veikia ne tik kaip barjeras, bet ir kaip sudėtinga, dinamiška sistema, sudaryta iš įvairių ląstelių tipų, tokių kaip virpamosios ląstelės, taurinės ląstelės ar bazinės ląstelės. Dar daugiau, pažanga pavienių ląstelių RNR sekoskaitoje dar labiau atskleidė šio audinio sudėtingumą, nustatant papildomus ląstelių tipus, tokius kaip jonocitai, deuterosomos, neuroendokrininės, kuokštinės, klubinės ląstelės ir gleives išskiriančios virpamosios ląstelės. Šios ląstelės, veikdamos kartu, siekia išlaikyti kvėpavimo takų homeostazę per įvairius mechanizmus, įskaitant mukociliarinį klirensą, gleivių gamybą, kvėpavimo takų pažaidų gydymą ir imuninį valdymą. Epitelio barjero sutrikimai gali prisidėti prie kvėpavimo takų ligų, tokių kaip astma, vystymosi, pabrėžiant šių sudėtingų ląstelinių santykių supratimo svarbą kuriant tikslinį pacientų gydymą. Epitelio sluoksnio kompleksiškumasir įvairialypumas yra itin svarbus kvėpavimo takų homeostazei bei astmos patofiziologijai, kur epitelio remodeliacija ir jo barjero disfunkcija yra viena iš pagrindinių sudedamųjų dalių. Taip pat, naujų ląstelių, pasižyminčių tiek virpamųjų, tiek taurinių ląstelių funkcijomis, identifikavimas astmos metu suteikia naujų įžvalgų apie ligos patogenezę ir galimus terapinius taikinius. Epitelio barjero vientisumas, kuris yra išlaikomas glaudžiųjų ir adhezinių jungčių dėka, yra būtinas, norint apsaugoti vidinius audinius nuo neigiamų išorinės aplinkos veiksnių. Tačiau, sergant astma, šis barjeras yra pažeidžiamas, todėl padidėja įkvepiamų patogenų pralaidumas, vystosi kvėpavimo takų hiperreaktyvumas, uždegimas ir kvėpavimo takų remodeliacija. Nepaisant mokslinių tyrimų astmos tematika pažangos, naujų astmos patogenezės koncepcijų poreikis išlieka, ypač norint paaiškinti 2 tipo uždegimo paradigmos trūkumus, apibrėžiant ryšio tarp kvėpavimo takų uždegimo ir remodeliacijos sąsajas. Supratimas apie molekulinius mechanizmus, lemiančius epitelio barjero disfunkciją, galėtų sudaryti sąlygas naujiems astmos gydymo būdams, skirtiems stiprinti barjero vientisumą ir galiausiai pagerinti pacientų gydymo rezultatus.
Reikšminiai žodžiai: epitelis, astma, struktūrinės ląstelės, barjerinė disfunkcija, kvėpavimo takų remodeliacija.

DOI: https://doi.org/10.37499/PIA.1425

INTRODUCTION

Asthma stands as a prevalent chronic respiratory condition, significantly impacting global health with its extensive morbidity and mortality. Characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, asthma's clinical manifestations vary widely among individuals, reflecting its complex pathophysiology and the diversity of its types and phenotypes. The global burden of asthma is substantial, affecting millions of individuals worldwide

and contributing to a significant number of deaths annually (1, 2). This variability in asthma's clinical presentation is underpinned by different phenotypic classifications, including, but not limited to, allergic (atopic) asthma, non-allergic asthma, exercise-induced bronchoconstriction, and aspirin-exacerbated respiratory disease, each with unique triggers and underlying mechanisms (3).

Airway remodeling, a hallmark of asthma, involves structural changes in the bronchial walls, including epithelial shedding, subepithelial fibrosis, increased smooth muscle mass, and neovascularization. These changes contribute to airway hyperresponsiveness, narrowing, and ultimately to the functional impairment observed in asthma (4). Central to asthma's inflammatory process are eosinophils, which play a pivotal role in allergic asthma and are a key target for some of the latest therapeutic interventions. The presence of eosinophils in the airways, along with other inflammatory markers, helps define asthma's eosinophilic phenotype, which is associated with more severe disease and is a predictor of responsiveness to certain treatments (5).

Recent advances in understanding the role of the bronchial epithelium have opened new avenues for asthma management. Once considered a passive barrier, the bronchial epithelium is now recognized as an active player in asthma pathogenesis, contributing to immune responses, airway inflammation, and remodeling through its interactions with environmental factors, allergens, and pathogens. This new approach to asthma, focusing on the bronchial epithelium, promises to unravel novel therapeutic targets and strategies, potentially transforming asthma care (6, 7).

This review aims to explore the current understanding of asthma, emphasizing the emerging role of the bronchial epithelium in its pathogenesis. By integrating insights into asthma's prevalence, types, phenotypes, and the traditional focus on eosinophils and airway remodeling, we set the stage for discussing how a deeper understanding of the bronchial epithelium can lead to innovative approaches to treatment and management, offering hope for better outcomes for individuals living with asthma.

METHODS

The scientific review provides information from freely available foreign scientific periodicals with a citation rate in the Clarivate Analytics Web of Science, Scopus, and Springerlink databases. The information was collected using National Center for Biotechnology Information (NCBI) PubMed and PMC, Google Scholar, and the Wiley Online Library search systems. The following keywords were used to collect the information: asthma, epithelium, structural cells, epithelium barrier, barrier dysfunction, airway remodeling. The exclusion criteria used for selecting scientific periodicals was non-peer reviewed sources, non-English articles, irrelevant subject matter, low citation impact.

THE CHANGING CONCEPTION OF ASTHMA PATHOPHYSIOLOGY

A wide range of treatments for asthma includes bronchodilators and anti-inflammatory medications, which cover immunosuppressive agents as well. These treatments are informed by the evolution of our understanding of asthma's pathogenesis, dating back to the time of Hippocrates. Yet, the pressing need for fresh perspectives on asthma's pathogenesis remains, especially as the current T helper 2(Th2)-dominant paradigm falls short in clarifying the disconnect between airway inflammation and remodeling, not to mention its inadequacy in addressing the rise in severe and treatment-resistant forms of asthma. This gap underscores the necessity for innovative concepts in understanding asthma that could illuminate these pathological aspects, laying the groundwork for new therapeutic approaches for severe and resistant asthma. Interestingly, the treatments we have today also reflect a shift from earlier understandings of asthma's origins. The term "asthma" itself, coined by Hippocrates, suggests "panting" or "gasping". Historical treatments ranged from symptom alleviation and modifying external factors with plant extracts, lifestyle adjustments, surgeries, or hypnosis, to inhaling "asthma cigarette" smoke containing substances like atropine and cocaine. The neuro-psychogenic theory of asthma once had wide acceptance, leading to the use of medications like chlorpromazine (8). Sir William Osler, in 1892, identified asthma as a bronchial muscle spasm, paving the way for bronchodilators and inhaled beta-agonists in the early 20th century. The latter half of the century recognized asthma primarily as an inflammatory disease, with corticosteroids emerging as the leading anti-inflammatory treatment. Though leukotriene receptor antagonists are not as effective as corticosteroids, they serve as supplementary treatments by blocking bronchoconstriction and inflammation. Current treatments primarily targeting inflammation fail to improve lung function or prevent exacerbations, pointing to the role of other factors like airway remodeling (8-10). Recent theories suggest that disruptions in airway epithelial integrity could be early indicators of asthma, challenging the belief that chronic inflammation is the precursor to airway remodeling. This new focus on epithelial changes as central to asthma pathogenesis demands further exploration, especially against the backdrop of the Th2-centric view. The significance of epithelial injury and remodeling in

asthma is acknowledged, but the mechanisms behind these changes remain underexplored (Figure 1). Initially thought to be secondary to inflammation, it's becoming clear that Th2-driven inflammation alone does not account for asthma's complexity, highlighting the critical role of the airway epithelium in asthma's pathogenesis and the urgency of deeper mechanistic studies (11).

Each of these theories has contributed valuable insights, proving true within their own contexts and timeframes. However, as new data emerge, particularly regarding the roles of airway epithelium and structural cell changes, it becomes evident that these earlier models, while accurate to an extent, were not comprehensive. This evolving landscape of asthma research has necessitated the development of new concepts that integrate older theories with groundbreaking discoveries. These advancements challenge us to rethink traditional paradigms and embrace a multifaceted approach to asthma, which not only considers inflammatory processes but also the critical interplay of cellular and structural dynamics within the airways.

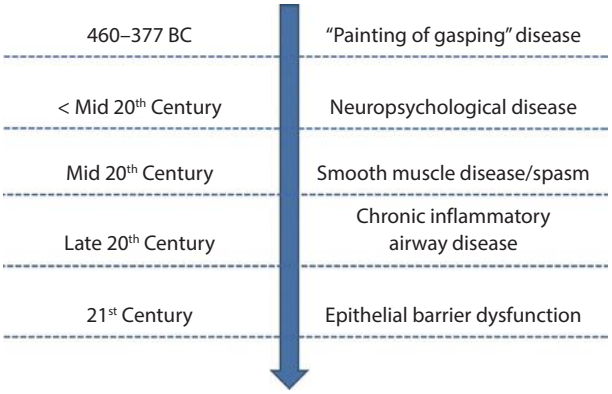

Figure 1. Evolving concepts of asthma

THE HETEROGENEITY OF BRONCHIAL EPITHELIUM

The bronchial epithelium acts as the first line of defense against the myriad of environmental insults, such as pollutants, pathogens, and allergens, that the respiratory system faces on a daily basis. This pseudostratified layer is not just a simple barrier but a complex, dynamic system comprising a variety of cell types, each contributing uniquely to its protective and regulatory functions. The primary cell types include ciliated cells, mucus-producing goblet cells, and basal cells. However, advancements in single-cell ribonucleic acid (RNA) sequencing technology have revealed a greater cellular diversity, identifying additional players like ionocytes, neuroendocrine cells, tuft cells, deuterosomal cells, and club cells, thereby enriching our understanding of the airway epithelium's complexity and functionality (Figure 2).

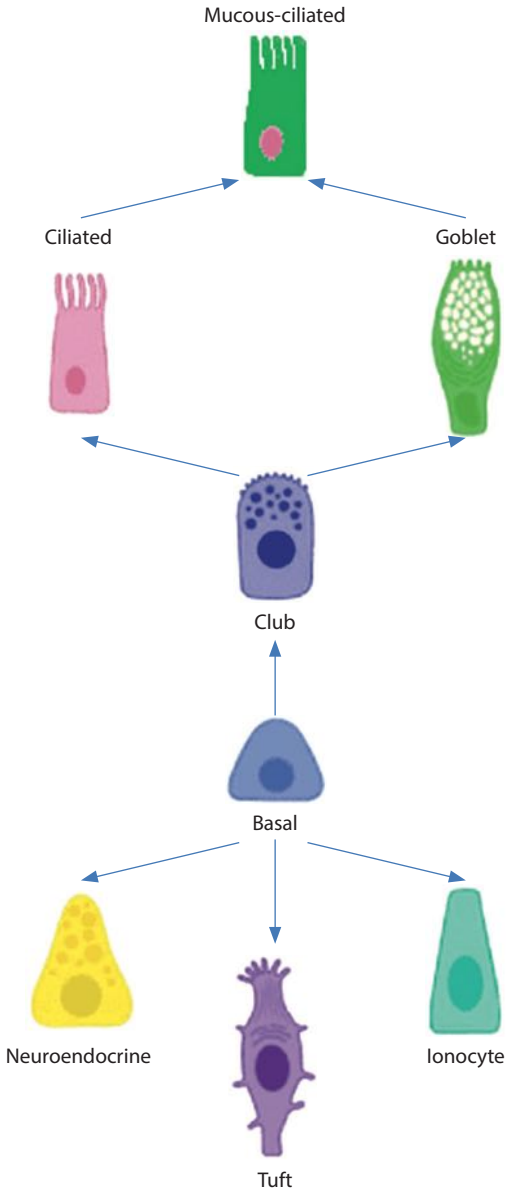

Figure 2. The heterogeneity of bronchial epithelial cells

Ciliated Cells: These cells are equipped with hair-like structures known as cilia that beat in a coordinated fashion to move mucus and trapped particles upwards towards the throat, from where they can be expelled or swallowed. This mechanical cleansing process, often referred to as the mucociliary escalator, is crucial for keeping the airways clear of mucus and debris, thus preventing infection and maintaining pulmonary health (12, 13).

Goblet Cells: Named for their goblet-like shape, these cells are responsible for the production and secretion of mucins, the primary components of mucus. Mucins are large glycoproteins that can trap pathogens, allergens, and particulates, facilitating their removal from the airway. The balance in mucus production and clearance is vital; an imbalance can lead to diseases such as chronic bronchitis, characterized by

excessive mucus production, or cystic fibrosis, where mucus becomes too thick and sticky to be effectively cleared (14, 15).

Basal Cells: Serving as the stem cells of the airway epithelium, basal cells lie at the base of the epithelial layer. They possess the remarkable ability to differentiate into various other epithelial cells, playing a pivotal role in the repair and regeneration of the airway lining following injury. Basal cells are also involved in sensing changes in the airway environment and initiating appropriate responses to maintain epithelial integrity (16, 17).

Ionocytes: Recently identified by single-cell RNA sequencing, ionocytes are rare but significant due to their high expression of the cystic fibrosis transmembrane conductance regulator gene. They are involved in regulating airway surface liquid pH and volume, critical for effective mucociliary clearance and antibacterial activity (18).

Neuroendocrine Cells: These cells are part of the airway's diffuse neuroendocrine system and are involved in sensing the airway environment and modulating local immune and inflammatory responses. They can release a variety of neuropeptides and bioactive amines in response to stimuli, influencing airway tone, growth, and inflammation (19).

Tuft Cells: Characterized by their distinctive "tuft" of microvilli, these chemosensory cells can detect chemical stimuli and are thought to play roles in immune modulation and epithelial signaling, potentially responding to parasitic infections and contributing to asthma pathogenesis (18).

Deuterosomal and Club Cells: Deuterosomal cells are a transitional form in the differentiation of basal cells into multiciliated cells, playing a key role in ciliogenesis. Club cells, previously known as **Clara cells**, contribute to the detoxification of harmful substances inhaled into the lungs, secrete components of the surfactant that reduces surface tension, and participate in the repair of the airway epithelium (20, 21).

The distribution and ratio of these diverse cell types along the airways are finely tuned to meet the local requirements for optimal respiratory function. Disruption in this delicate balance can contribute to the pathogenesis of various respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), and chronic rhinosinusitis with nasal polyps, where abnormal epithelial remodeling and dysfunction play a central role. Understanding the intricate relationships and functions of these cell types within the bronchial epithelium not only sheds light on the basic mechanisms of respiratory health but also opens new avenues for the development of targeted therapies aimed at restoring epithelial function in respiratory diseases. Moreover, Vieira Braga with colleagues outlines a significant advancement in understanding the cellular landscape of the human lung, particularly in the context of asthma (12). Among the notable discoveries is the identification of a novel mucous ciliated cell state, highly enriched in the lungs of asthmatic patients. These mucous ciliated cells represent a unique transitional state of ciliated cells, contributing to mucous cell hyperplasia, a hallmark of asthma's chronic disease state. Unlike typical ciliated cells, mucous ciliated cells co-express genes typically associated with both ciliated and goblet cells, such as FOXJ1 (a marker for ciliated cells) and MUC5AC (a mucin gene associated with goblet cells), alongside CEACAM5. This finding suggests that the mucous ciliated cell state may play a crucial role in the excessive mucus production observed in asthma, offering new insights into the disease's pathogenesis and potential targets for therapeutic intervention (12).

EPITHELIAL BARRIER

The airway epithelium acts as a critical barrier in the respiratory system, providing the first line of defense against environmental insults, including allergens, microbes, and pollutants. This barrier is crucial for maintaining pulmonary homeostasis and plays a significant role in the pathogenesis of various respiratory diseases, including asthma (22).

The primary function of the epithelial barrier is to protect the underlying tissue from potential threats while maintaining tissue homeostasis. This is achieved through a combination of physical, chemical, and immunological mechanisms. The airway epithelial cells line the respiratory tract from the trachea to the terminal bronchioles and are equipped with cilia and mucus to trap and expel inhaled particles. These cells also regulate water and ion transport to keep the airways moist and facilitate mucociliary clearance. In the context of asthma, the regulation of the airway epithelial barrier function emerges as a crucial checkpoint. Asthmatic conditions compromise the respiratory epithelium, evidenced by abnormal antimicrobial response patterns and structural alterations in the epithelium, which may precede the onset of airway inflammation (23).

The integrity of the epithelial barrier is maintained by tight junctions (TJs) and adherens junctions (AJs), which control the paracellular transport and provide mechanical strength to the epithelium. Key components include transmembrane proteins such as claudins, occludin, and E-cadherin, which interact with the cytoskeleton to seal the space between adjacent cells and regulate barrier permeability. Disruption of the epithelial barrier function in asthma is evident through increased permeability to allergens,

detachment of ciliated cells, and reduced expression of cell-cell adhesion molecules such as E-cadherin. This impairment is associated with airway hyper-responsiveness, inflammation, and remodeling, emphasizing the central role of epithelial barrier dysfunction in asthma pathogenesis (24).

Inflammatory cytokines and environmental factors can further exacerbate barrier dysfunction, leading to increased susceptibility to infections and heightened inflammatory responses. For instance, exposure to allergens like house dust mites can directly cleave epithelial junction proteins or activate pattern recognition receptors, inducing barrier dysfunction through a cascade of intracellular signaling pathways (25-27).

Understanding the molecular mechanisms underlying epithelial barrier dysfunction and its regulation offers potential for novel therapeutic strategies in asthma and related respiratory conditions. Targeting pathways involved in maintaining or restoring epithelial barrier function could lead to the development of treatments aimed at enhancing barrier integrity, thereby mitigating the severity of asthma and improving patient outcomes. Targeting the airway epithelial barrier presents a viable and innovative therapeutic strategy for asthma and related allergic diseases, given the pivotal role intrinsic abnormalities in the airway epithelium play in fostering inappropriate immune responses and defective repair mechanisms. The exploration of genetically supported targets and pathways that contribute to maintaining or enhancing epithelial barrier function, including those improving mucosal innate immunity, enhancing tight junction and adherens junction protein assembly, and promoting epithelial cell integrity – offers substantial potential (28-30). Recent advancements, such as the inhibition of β-catenin/CBP signaling to prevent epithelial-mesenchymal transition and enhance barrier recovery, along with the modulation of Notch signaling impacting mucus secretion, underline the efficacy of targeting molecular pathways to correct epithelial dysfunctions (31). Despite the widespread use of inhaled corticosteroids and bronchodilators, their direct impact on epithelial health remains ambiguous, with evidence suggesting varied responses in asthmatic epithelium, particularly under oxidative stress and inflammatory conditions. Future therapeutic strategies should consider combining these treatments with novel agents like biologics targeting type-2 cytokines and interventions to restore corticosteroid sensitivity, potentially offering enhanced protection and repair of the epithelial barrier in asthma management.

EPITHELIUM BARRIER DYSFUNCTION

In asthma, the integrity of the airway epithelial barrier is significantly compromised, manifesting through several pathological features such as the detachment of ciliated cells, the presence of epithelial cell clusters known as creola bodies within the sputum, an increased permeability to various allergens, and a notable reduction in the expression of the cell-cell adhesion molecule E-cadherin (32, 33). This disruption is observed across all asthma phenotypes, marking epithelial damage as a universal characteristic of the condition (34). Furthermore, structural alterations within the airway epithelium of children facing respiratory difficulties have been documented even before the clinical onset of airway inflammation and the formal diagnosis of asthma, indicating that such epithelial changes are among the earliest events in the disease's pathogenesis (35). This observation challenges the long-held belief that chronic airway inflammation is the precursor to airway remodeling.

Asthmatic airway remodeling is characterized by a significant loss of proteins responsible for maintaining cell-cell contact, essential for preserving the structural integrity of the epithelial barrier. These proteins include TJs, AJs, and desmosomes, with TJs located at the most apical regions and AJs and desmosomes situated basolaterally (36). Desmosomes provide adhesive bonds between adjacent cells or between cells and the lamina propria through non-classical cadherins. E-cadherin, a transmembrane protein, forms the core of AJs; its extracellular domain homotypically binds to neighboring cells, while its intracellular domain connects to the actin cytoskeleton via a network of catenin proteins, providing both mechanical support and facilitating intracellular signaling (36). The disruption of E-cadherin leads to the mislocalization of TJ proteins, highlighting its crucial role in the formation and maintenance of epithelial junctions (37). TJs comprise transmembrane proteins such as zona occludens-1, occludin, claudins, and junction adhesion molecules, playing a pivotal role in regulating epithelial permeability (24). In asthma patients, the expressions of E-cadherin, β-catenin, zona occludens-1, and occludin are disrupted (33, 38), contributing to a compromised barrier function.

Animal models have demonstrated that lung epithelial-specific deficiency in E-cadherin not only leads to epithelial denudation but also specifically targets the loss of ciliated cells (30). Furthermore, when E-cadherin is lost in club cells, it triggers their proliferation while inhibiting differentiation, thus impairing the epithelial repair mechanisms following injury (39). The significance of E-cadherin extends beyond the formation of a structurally intact epithelial layer; its downregulation is also pivotal for epithelial plasticity. This process, known as epithelial-to-mesenchymal transition (EMT), involves cells losing their epithelial characteristics and acquiring

mesenchymal features (40). The loss of E-cadherin releases β-catenin into the cytoplasm, where it typically undergoes proteolytic degradation. However, the inactivation of glycogen synthase kinase -3β, through pathways such as active wingless/integrated signaling or transforming growth factor- β (TGF-β), prevents this degradation, allowing β-catenin to translocate to the nucleus and activate transcription. This activation promotes the expression of E-cadherin repressors and various mesenchymal genes, contributing to airway wall remodeling (36).

The initiation of a mesenchymal phenotype is critical for epithelial repair, fostering cell migration and proliferation. However, in asthma, this repair mechanism is often disrupted, as evidenced by an increase in markers of basal cells and repair, suggesting a more proliferative yet less differentiated phenotype. The exposure to house dust mite not only facilitates TGF-β-induced EMT in airway epithelial cells *in vitro* but also induces EMT-like features in the airway epithelium of mice, underscoring the heightened susceptibility of asthmatic epithelial cells to undergo TGF-β-induced EMT (41, 42). The Notch signaling pathway is crucial in determining the fate of airway epithelial cells post-injury, although the mechanisms through which it affects epithelial homeostasis and response to environmental insults remain to be fully elucidated (43).

The failure to properly reconstitute epithelial barrier function following damage carries significant pathophysiological consequences. It not only results in increased permeability to allergens but also perpetuates pro-inflammatory and abnormal repair responses within the airways. These changes contribute to airway hyperresponsiveness and remodeling (44), with airway epithelial damage correlating directly with the severity of airway hyperresponsiveness (45). Moreover, the knockdown of E-cadherin *in vitro* has been shown to result in epidermal growth factor receptor activation and pro-inflammatory responses. The *in vivo* loss of E-cadherin and subsequent loss of ciliated cells is accompanied by spontaneous goblet cell metaplasia and the infiltration of eosinophils and dendritic cells (36), potentially mediated by β-catenin activation. Inhibition of downstream β-catenin activity has been shown to mitigate airway inflammation and remodeling in asthma mouse models, and recent studies suggest that inhibiting β-catenin/Creb binding protein signaling not only enhances epithelial barrier function but also attenuates pro-inflammatory responses induced by house dust mite exposure *in vitro* (31).

CONCLUSIONS

In conclusion, the current review underscores the dynamic and complex nature of asthma, shifting the focus from its traditional understanding as a disease primarily driven by Th2-dominant inflammation to a multifaceted disorder where airway epithelium integrity plays a pivotal role. Our journey from historical treatments and theories to the latest advancements in cellular biology reveals asthma as a disease shaped by both its inflammatory and structural components, with significant implications for treatment and management. The identification of the diverse cell types within the bronchial epithelium and their unique contributions to asthma pathogenesis, alongside the critical role of epithelial barrier dysfunction, represents a paradigm shift in our understanding of the disease. This comprehensive view acknowledges the heterogeneity of asthma, emphasizing the necessity for targeted therapies that address not only inflammation but also repair and maintenance of epithelial barrier function. As we delve deeper into the mechanisms behind epithelial damage and its relation to asthma severity, the potential for novel therapeutic interventions emerges, offering hope for more effective management strategies for those suffering from this chronic condition. Future research must continue to explore the intricate interactions between epithelial cells, immune responses, and environmental factors, aiming to unravel the complex web of asthma pathogenesis. This endeavor will not only refine our current treatment approaches but also pave the way for innovative strategies that could one day transform the lives of millions affected by asthma worldwide. Future research into epithelial barrier dysfunction in asthma could focus on elucidating the roles and interactions of tight junctions and adherens junctions, particularly exploring therapeutic interventions aimed at enhancing barrier integrity. Investigating how environmental and genetic factors influence barrier function could lead to personalized asthma management strategies. Advancements in single-cell RNA sequencing could help identify new cellular players in epithelial barrier dysfunction, offering insights into disease mechanisms and potential therapeutic targets. Longitudinal studies tracking the progression of epithelial barrier dysfunction from early stages could provide valuable data on critical intervention points. Finally, initiating clinical trials to test barrier-enhancing therapies could evaluate their efficacy in reducing asthma exacerbations and improving patient outcomes.

Gauta 2024 04 05
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