## Mechanisms of allergic diseases

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# Breakdown in epithelial barrier function in patients with asthma: Identification of novel therapeutic approaches

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**Overall Purpose/Goal:** To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

**Target Audience:** Physicians and researchers within the field of allergic disease.

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**Activity Objectives**

1. To understand the role of the bronchial epithelium as a chemical, physical, and immunologic barrier to the inhaled environment.
2. To recognize abnormalities in barrier function in patients with asthma.
3. To recognize potential therapeutic approaches to restore barrier function.

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**The bronchial epithelium is pivotally involved in the provision of chemical, physical, and immunologic barriers to the inhaled environment. These barriers serve to maintain normal homeostasis, but when compromised, the immunologic barrier becomes activated to protect the internal milieu of the lung. We discuss what is currently understood about abnormalities in these barrier functions in patients with asthma and consider novel therapeutic opportunities that target this key structure. (J Allergy Clin Immunol 2009;124:23-34.)**

***Key words:*** *Asthma, epithelium, tight junction, innate immunity, permeability, allergen, virus*

*Abbreviations used*
BEC: Bronchial epithelial cell
DC: Dendritic cell
EGF: Epidermal growth factor
IP-10: IFN-inducible protein 10
MC: Mast cell
TJ: Tight junction
TLR: Toll-like receptor
ZO: Zonula occludens

Asthma is an inflammatory disorder of the conducting airways, which undergo distinct structural and functional changes, leading to nonspecific ***bronchial hyperresponsiveness*** and airflow obstruction that fluctuates over time. It is among the most common chronic conditions in Western countries, affecting 1 in 7 children and 1 in 12 adults. Although at one time considered a single disease entity, asthma subphenotypes are now recognized with differing pathology, clinical expression, responses to treatment, and long-term outcomes.[1] Most asthma exhibits a $T_H2$-type inflammatory response with upregulation of cytokines of the *IL4* gene cluster linked to ***atopy***; however, the indistinguishable pathologic features of nonallergic and allergic asthma and the fact that the great majority of atopic subjects do not have asthma[2] emphasizes that asthmatic airway inflammation and remodeling can occur independent of atopy.[3]

We have previously proposed that allergic-type inflammation and aberrant epithelial injury/repair mechanisms were parallel

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Terms in boldface and italics are defined in the glossary on page 24.

phenomena leading to different asthma subtypes[4] that involved activation of the epithelial-mesenchymal trophic unit, which controls the local tissue microenvironment.[5] We postulated that in patients with asthma, epithelial susceptibility to damage by environmental agents results in signals that act on the underlying mesenchyme to propagate and amplify inflammatory and remodeling responses in the submucosa. Based on current understanding, many of the persistent inflammatory and structural responses in patients with asthma, including airway allergen sensitization in genetically susceptible individuals, could follow from a defective epithelium, leading to a chronic wound response to repeated environmental injury. Similar mechanisms are now thought to operate in other allergic diseases, leading to enhanced allergen sensitization. Examples include eczema, in which ***polymorphisms*** in the ***filaggrin*** gene affect skin permeability,[6] and food allergy, in which infection or stress can increase intestinal permeability.[7]

The finding that many novel asthma susceptibility genes identified from hypothesis-independent approaches[8] are expressed in the epithelium helps place it at the center of asthma pathogenesis. Furthermore, the most frequent environmental risk factors for developing, exacerbating, and prolonging asthma, namely biologically active allergens, air pollutants, environmental tobacco smoke, and respiratory viruses,[9-11] act on the epithelium, thereby strengthening the case for a dynamic interaction between the epithelium and formed elements of the airways in the development of asthma subphenotypes.[1] The purpose of this

## GLOSSARY

**ANTIOXIDANTS:** antioxidants are molecules capable of slowing or preventing the oxidation of other molecules by removing free radical intermediates. They are separated into hydrophilic or hydrophobic antioxidants depending on whether they are soluble in water or in lipids, respectively. Generally, hydrophilic antioxidants react with oxidants in the cell cytosol and the blood plasma, whereas hydrophobic antioxidants protect cell membranes from lipid peroxidation.

**ATOPY:** Atopy is most commonly defined by increased levels of total and allergen-specific IgE in the serum, leading to positive skin prick test responses to common allergens. Atopy also refers to the genetic tendency for the classic allergic diseases: atopic dermatitis, allergic rhinitis (hay fever), and asthma.

**BRONCHIAL HYPERRESPONSIVENESS:** Bronchial hyperresponsiveness is also known as airway hyperreactivity. It is an exaggerated constriction of the bronchioles or small airways of the lung in response to physical, chemical, or pharmacologic stimuli. It is typically assessed based on a bronchial challenge test with methacholine or histamine. Bronchial hyperresponsiveness is a hallmark of asthma but also occurs in subjects with chronic obstructive pulmonary disease.

**COMPLEMENT:** Complement is a biochemical cascade of more than 20 proteins that aid in eliminating pathogens as part of the innate immune response. The complement cascades function to (1) lyse cells, bacteria, and viruses; (2) promote phagocytosis of pathogens by means of opsonization; (3) bind to complement receptors to trigger downstream events; and (4) remove immune complexes. The classical complement pathway, alternative complement pathway, and mannose-binding lectin pathway carry out these functions.

**DENDRITIC CELL:** DCs are immune cells that take up, process, and present antigen to other immune cells, namely T and B cells in lymphoid tissue. These antigen-presenting cells are primarily found in tissue that serves as an entry point for antigen (ie, skin, lungs, and intestines). DCs are derived from hemopoietic bone marrow progenitors and can be plasmacytoid (pDC) or myeloid (mDC).

**FILAGGRIN:** Filament aggregating protein (filaggrin) is a key protein that binds to and causes the aggregation of keratins (K1/10). Loss-of-function (null) mutations in the gene encoding filaggrin *(FLG)* result in impaired skin barrier function (ie, ichthyosis vulgaris, atopic dermatitis, or both) and are strongly associated with the development of asthma in patients with atopic dermatitis. R501X and 2284del4 are the most common mutations in the white population, with a prevalence of approximately 7% to 10%.

**HAPLOTYPE:** A haplotype is a combination of alleles within close proximity on the same chromosome that tend to be inherited together. It can range from as few as 2 loci or as much as an entire chromosome depending on the number of recombination events.

**LAMINA PROPRIA:** The lamina propria is part of the mucosa, which lines the respiratory tract, the gastrointestinal tract, and the urogenital tract. More specifically, the lamina propria is a thin layer of loose connective tissue that, combined with the epithelium, forms the mucosa.

**MAST CELL:** MCs reside in various tissues throughout the body and contain histamine and heparin-rich granules. Degranulation can be initiated by means of direct injury, cross-linking of IgE receptors, or activated complement proteins. In addition to allergy and anaphylaxis, MCs exhibit a protective role by being involved in wound healing and defense against pathogens.

**MUCIN:** Mucins are a class of approximately 19 proteins produced by epithelial tissues. The aminoterminal and carboxyterminal regions of mucin proteins are lightly glycosylated and rich with cysteines to facilitate the formation of disulfide linkages. The central region of mucin proteins is primarily saturated with O-linked oligosaccharides. Increased mucin production is seen in patients with asthma, bronchitis, and chronic obstructive pulmonary disease, with MUC5AC and MUC5B as the most prevalent.

**POLYMORPHISM:** A polymorphism is also referred to as a single nucleotide polymorphism (SNP) and is a genomic variation occurring when a single nucleotide is different between members of the same species. SNPs can alter genomic DNA-coding sequences, thereby potentially altering amino acid sequences and protein production. In genetic studies SNPs are often assigned an allelic frequency and can be used as biomarkers to determine whether a patient has a genetic predisposition for a particular disease.

**REACTIVE OXYGEN SPECIES:** Reactive oxygen species are oxygen centered free radicals or reactive non-radical compounds that are generated enzymatically or form as a byproduct of oxygen metabolism and can increase dramatically in times of environmental stress. Reactive oxygen species can induce significant cell damage by damaging DNA, oxidizing fatty acids in lipids, oxidizing amino acids, and inactivating specific enzymes.

**TIGHT JUNCTION:** A TJ is a closely associated area of 2 cells with membranes that join together, forming a virtually impermeable barrier to fluid. TJs prevent the passage of molecules and ions through the space between cells, thereby forcing them to enter the cells by means of diffusion or active transport to pass through the tissue. Movement of membrane proteins between the apical and basolateral surfaces of the cell is additionally blocked, preserving transcellular transport.

**THYMIC STROMAL LYMPHOPOIETIN:** TSLP is produced mainly by nonhematopoietic cells as fibroblasts, epithelial cells, and different types of stromal or stromal-like cells. By signaling through the heterodimeric receptor complex of TSLP receptor and IL-7 receptor $\alpha$, TSLP triggers the release of T cell–attracting chemokines from monocytes and the maturation of DCs. Expression of TSLP is enhanced under atopic conditions, potentiating a $T_H2$ response.

**TOLL-LIKE RECEPTORS:** TLRs are a family of membrane glycoproteins that play an important role in the innate immune response by recognizing pathogen-associated molecular patterns, molecules that are shared by pathogens but distinguishable from host molecules. Thirteen TLRs have been identified in human subjects and mice collectively and pair with an adaptor molecule for signaling. TLRs are members of a larger superfamily that includes the IL-1 receptors because of a conserved Toll/IL-1 receptor domain in the cytoplasmic tail.

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