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Asthma and allergy: The emerging epithelium

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Abstract

Thinking about how asthma and allergic diseases arise is undergoing several shifts. In ‘Bedside to Bench’, Clare M. Lloyd and Sejal Saglani examine how recent human studies are putting the focus on the epithelium as a major contributor to asthma. The findings shift the emphasis away from the T helper type 2 immune response, and call into question the utility of current animal models of the disease. Although asthma and other allergic disorders are known to have origins in infancy, some researchers are looking even earlier, to effects *in utero* and before conception. In ‘Bench to Bedside’, Catherine Hawrylowicz and Kimuli Ryanna highlight animal studies that outline some of the effects of the maternal environment, and they examine the potential implications for prevention of disease.

Asthma is classically considered a disorder of the immune system. People with the disease typically show a T helper type 2 (T_H2) type inflammatory profile, indicative of overactive allergic antibody responses. Given this phenotype, investigations of new treatment strategies have targeted mainly T_H2 cytokines and downstream cells and mediators. But several strands of evidence are calling this approach into question.

Genetic studies, such as a recent report linking asthma to an adhesion molecule on the airway epithelium¹, have strengthened the idea that aberrant expression of genes within the epithelium is a key driver of the allergic response. Meanwhile, results from trials targeting the T_H2 response, such as recent studies examining interleukin-5 (IL-5)-blocking antibodies^{2,3}, have been underwhelming. In parallel, other studies have confirmed the presence of various asthma phenotypes; Moore *et al.*⁴, for instance, pinpoint five. Together, such data suggest that the various forms of asthma are driven by distinct pathological mechanisms, many originating in the epithelium. Perhaps it is time for researchers at the bench to approach their mechanistic work in another way and rethink the design of preclinical models of the disease.

In the last few years, a number of genes expressed in the pulmonary epithelium have been shown to segregate with asthma^{5,6}. In a more recent entry into this area, Koppelman *et al.*¹ home in on the gene encoding protocadherin-1 (*PCDHI*), an adhesion molecule on the airway epithelium. *PCDHI*, they discover, is a susceptibility gene for airway hyperresponsiveness, a key feature of asthma¹. These findings strengthen the idea that asthma occurs as a result of aberrant gene expression within the epithelium and that structural cells are key drivers of the allergic response.

The pulmonary epithelium not only provides a barrier between the outside environment and internal parenchyma but also responds to microbes and noxious stimuli that overcome the mucociliary barrier, and it is therefore vital for host defense. This barrier function is impaired in asthma, with disruption of tight junctions and increased epithelial permeability. Apart from providing a physical barrier, the pulmonary epithelium is immunologically active. It is pivotal in the development of immune responses in the lung⁷. Pulmonary epithelial cells are in intimate physical contact with the immune system and secrete a wide range of cytokines and chemokines, and these cells sense microbes via pattern recognition receptors such as the Toll-like receptors. Epithelial cells can also secrete a range of antimicrobial mediators including lysozyme, defensins, collectins and complement components. Many of the molecules secreted by epithelial cells in response to microbial or allergen exposure have the ability to regulate immune reactions and recruit cells of the innate and adaptive immune system⁸. Therefore, the initiation and maintenance of inflammation at epithelial surfaces is induced by local mechanisms that have marked effects on the outcome of the immune response.

Interactions between the epithelium and the immune system are likely to be major drivers of disease initiation and progression. These interactions might also help explain the heterogeneity of asthma. The molecular basis for this heterogeneity is uncertain, but defining the gene signature of particular cells in asthma has proved revealing. The T_H2-induced genes *POSTN* (encoding periostin), *SERPINE2* (encoding Serpin peptidase inhibitor clade B, member 2) and *CLCA1* (encoding chloride channel accessory 2) have previously been identified as epithelial genes specifically induced in asthma and were proposed as an asthma-specific mRNA signature for epithelial cells⁹. A more recent study identifies at least two distinct molecular phenotypes of asthma defined by the degree of T_H2 inflammation¹⁰. These data strengthen the argument that epithelial function affects the degree of T_H2 inflammation.

In parallel, the clinical heterogeneity of asthma has been emphasized by unbiased statistical cluster analysis techniques. Moore *et al.*⁴ have described five distinct severe asthma phenotypes that differ in lung function, age of asthma onset, disease duration, atopy, gender, symptoms, medication use and health care usage. The existence of these distinct phenotypes suggests that several pathologic mechanisms promote the variety of symptoms. It would now be useful to analyze people with each phenotype with respect to their epithelial and immune markers to determine whether a molecular signature can be assigned to each clinical phenotype and thus provide clear direction for phenotype specific therapy.

Results from recent clinical trials for a blocking antibody against the T_H2 cytokine IL-5 support the presence of distinct asthma phenotypes. An effect was seen only in subjects with severe asthma resistant to standard treatments, requiring oral steroids and characterized by large numbers of eosinophils^{2,3}. It is likely that other T_H2 pathways being investigated in asthma as therapeutic targets will only be of benefit in such subjects. Those with low T_H2 responses, and with high numbers of other inflammatory cells, such as neutrophils, who represent at least a third of all severe asthmatics, have a relatively poor response to steroids and thus highlight a clear unmet clinical need.

Current preclinical models have focused almost exclusively on the role of T_H2-derived inflammation and do not adequately characterize asthma that is not driven by T_H2 responses. Developing new models is not straightforward, given that the mechanisms underlying the characteristic symptoms of non-T_H2 asthma are not well understood. But research points in the direction of factors associated with the innate immune system, such as environmental exposure to bacterial endotoxin, air pollution, ozone and infection history¹¹.

The growing body of genetic and clinical data highlight the need to consider the role of structural components of the airway in the onset and propagation of asthma. In particular, the epithelium may be central, as this surface is the first contact for allergens within the lung. The environment of allergen challenge must be taken equally into consideration. To reflect the described clinical phenotypes, new models must also take into account age, obesity and gender differences, to enable investigation of how these factors affect epithelial immune interactions after allergen exposure. The task now is to refine or redesign preclinical model systems to enable more effective translation of basic science findings into the clinic.

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Figure 1.

The clinical characteristics of asthma are classically heterogeneous. Although once thought to be a disease of aberrant T_H2 -directed immune responses, clinical studies indicate that individuals with asthma can be phenotyped according to their symptoms and that these clinical phenotypes are closely associated with environmental factors. Moreover, interaction between the epithelium and the immune system is crucial in driving disease, and the genetic signature of airway epithelial cells may influence clinical phenotype.