‘Bedside’ observations challenge aspects of the ‘epithelial barrier hypothesis’

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In his Review, Akdis explains the rise in prevalence of allergic and chronic inflammatory diseases by proposing that ‘leaky epithelial barriers’ caused by environmental toxins lead to colonization by opportunistic pathogens and to microbial dysbiosis, and that immune responses to pathogens promote further barrier defects in a vicious circle (Akdis, C. A. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat. Rev. Immunol.* https://doi.org/10.1038/s41577-021-00538-7 (2021))[1]. However, ‘bedside’ data in patients with asthma and allergic rhinitis argue against the idea of a leaky epithelial barrier in these conditions. The common expression ‘leaky epithelial barrier’ actually eclipses an important asymmetry of the barrier functions of human conducting airways.

Allergic rhinitis

The popular notion that increased nasal absorption of allergens occurs in individuals who are atopic was first tested in 1930. Contrary to expectations, decreased ‘absorption’ was observed[2]. With novel methods that control for potential confounding factors (mucosal surface concentration of absorption tracer, influence of mucociliary clearance, area of exposed airway mucosa and time of exposure), similar results were found in individuals suffering from perennial allergic rhinitis[3] and especially in active seasonal allergic rhinitis when, paradoxically, the outward penetrability of the nasal mucosal membrane to non-sieved plasma macromolecules was much increased[4,5].

Asthma

In asthma, exuded plasma-derived peptides/proteins (in the size range from small cathelicidins to the larger IgM) are increased in sputum[5,6]. However, it has been repeatedly demonstrated that absorption of inhaled tracers is not increased in individuals with asthma[5,7–9].

Preventing barrier defects in vivo

Epithelial cell loss is a feature of asthmatic bronchi[5]. Studies of asthma-like denudation in guinea pig tracheas have shown that loss of pseudostratified epithelium caused strictly localized plasma exudation that promptly produced, and sustained, a biologically active, fibrin–fibronectin gel barrier, which promoted optimal epithelial regeneration[5,10]. As soon as a barrier of undifferentiated repair epithelium was established, plasma exudation ceased and the fibrin–fibronectin gel was shed. Thus, barrier defects may be reduced, but there is a cost. The epithelial regeneration alone induced asthma-like eosinophilic–neutrophilic airway inflammation and remodelling[5].

Reconciling bench and bedside data

Whereas in vitro data may indicate defective airway epithelial barriers in asthma and rhinitis[1], observations in patients suggest well-maintained barrier functions. However, pseudostratified airway epithelial linings are asymmetric with regard to penetrability. As evidenced by permeability to macromolecules in response to slight increases in hydrostatic pressure, it is a poor barrier when approached from beneath[5,10]. This feature is key to the physiological cooperation between the ubiquitous, superficial airway mucosal microcirculation, carrying systemic blood, and the overlying epithelium, where the latter permits swift, non-sieved transmission of extravasated plasma proteins in airway allergic diseases[5,10]. Moreover, in airway infections, exudation of plasma macromolecules is observed until the resolution of symptoms, whereas tracer data suggested unchanged absorption permeability[6,10]. Hence, in environmentally induced airway inflammation, increased levels of plasma macromolecules appear on the surface of a mucosa with an intact barrier, suggesting that humoral responses participate in an early innate respiratory defense[5,6,10]. Whether a similar, direction-dependent epithelial barrier asymmetry also exists in the human gut is currently unclear[10].

Akdis stresses the need of further research on airway epithelial barriers[1]. In addition to the models discussed in his Review, in vivo models that specifically replicate the airway (not pulmonary[6]) plasma exudation, while retaining the barrier to allergens and tracers as observed in humans, seem warranted.

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1. Akdis, C. A. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat. Rev. Immunol.* https://doi.org/10.1038/s41577-021-00538-7 (2021).
2. Cohen, M. B. et al. The rate of absorption of ragweed pollen material from the nose. *J. Immunol.* **18**, 419–425 (1930).
3. Greiff, L. et al. Absorption across the nasal airway mucosa in house dust mite perennial allergic rhinitis. *Clin. Physiol. Funct. Imaging* **22**, 55–57 (2002).
4. Greiff, L. et al. Reduced airway absorption in seasonal allergic rhinitis. *Am. J. Respir. Crit. Care Med.* **156**, 783–786 (1997).
5. Persson, C. Airways exudation of plasma macromolecules: Innate defense, epithelial regeneration, and asthma. *J. Allergy Clin. Immunol.* **143**, 1271–1286 (2019).
6. Persson, C. Early humoral defence: Contributing to confining COVID-19 to conducting airways? *Scand. J. Immunol.* https://doi.org/10.1111/sji.13024 (2021).
7. O’Byrne, P. M. et al. Lung epithelial permeability: relation to non-specific airway responsiveness. *J. Appl. Physiol. Respir. Environ. Exerc. Physiol.* **57**, 77–84 (1984).
8. Del Donno, M. et al. Lung epithelial permeability and bronchial responsiveness in subjects with stable asthma. *Chest* **111**, 1255–1260 (1997).
9. Georas, S. et al. The leaky lung test: A pilot study using inhaled mannitol to measure airway barrier function in asthma. *J. Asthma* **56**, 1257–1265 (2019).
10. Persson, C. Humoral first-line mucosal innate defence in vivo. *J. Innate Immun.* **12**, 373–386 (2020).