**Epithelial Barrier Dysfunction in the Lower Airways**

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Why do we need tissue barriers?

- Multicellular organisms require tissue compartmentalization to support specialized functions.
- Cells that cover the external surface and line the internal compartments must form barriers to define boundaries and prevent unrestricted exchange of materials.
- The nature of the cells forming a particular barrier reflects the specialized function at that site.
- The functions of epithelia are related in some way to interaction between the internal and external environments of the body: eg. nutrition, gas exchange, excretion, or the intrusions and extrusions required for reproduction.

Marchiando AM et al Annual Review of Pathology 2010; 5: 119-144

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**Epithelia form Physical Barriers......and more**

- **Physical barrier**
  - Polarized (’fence’ and ’gate’ functions)
  - Trans- and para-cellular permeability
- **Chemical barrier**
  - mucus (mucosae)
  - host defence peptides
  - antioxidants
- **Immunological barrier**
  - Surveillance (PAMPs, DAMPs/alarmins)
  - Recruitment/activation of effector cells and antigen presenting cells

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**The Bronchial Epithelial Barrier**

- The airway epithelium is now appreciated as an important component of the innate immune system. It is constantly exposed to noxious inhaled agents and pathogens.
- As a fully differentiated, mucociliary epithelium, the bronchial epithelium acts as a physical and chemical barrier to protect the internal milieu of the lung.
- It is a testament to the effectiveness of the epithelial barrier that most environmental challenges are largely overcome without the need to develop an inflammatory response.
- As the initial cell of contact with the environment the bronchial epithelium is pivotal in immune surveillance and (appropriate) activation of effector cells and APCs.
- The bronchial epithelium controls tissue homeostasis – dysregulation of these mechanisms can contribute to disease pathologies.

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**The Bronchial Epithelial Barrier in Asthma**

- The physical barrier of the bronchial epithelium in asthma is disrupted (Xiao et al, JACI 2011)
- Functional studies using epithelial cultures from asthmatic or normal donors indicate that there is increased permeability and sensitivity to environmental challenges in asthma (Xiao et al, JACI 2011; Blume et al ERJ 2013)
- Epithelial susceptibility to environmental insults may lead to inappropriate activation of immune cells
- The immunological barrier in asthma is abnormal – there is a deficient innate immune response to RV infection (Wark et al, JEM 2005)
- This may explain why asthmatic subjects have increased susceptibility to the common cold virus and experience more severe lower respiratory tract symptoms (ie. exacerbations)

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**Asthma Susceptibility Genes – Links with Epithelial Immunity?**

Barrier properties?
- PCDH1
- CDHR3

Innate immune responses?
- CHODE-3.25ZDNL
- 4.31
- 1.1801
- TSLP