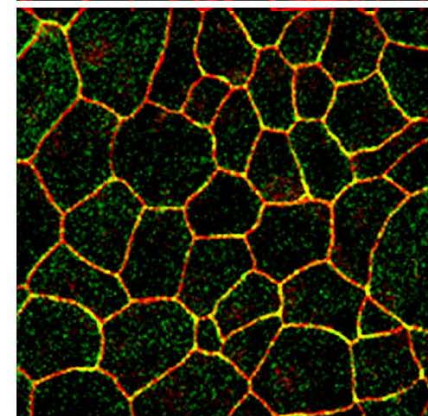
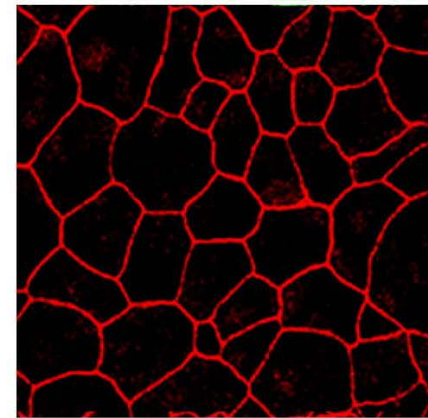
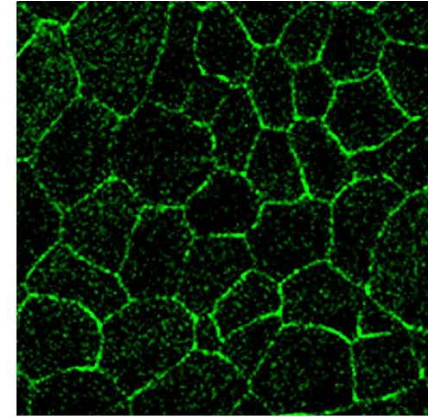


WISC 2014 *Rio de Janeiro, Brazil*
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WAO International Scientific Conference 2014 and the
XLI Annual Meeting of the Brazilian Association of Allergy and Immunology (ASBAI)



Epithelial Cells in Asthma Pathogenesis

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Overview

Asthma is the expression of allergic disease in the airways.

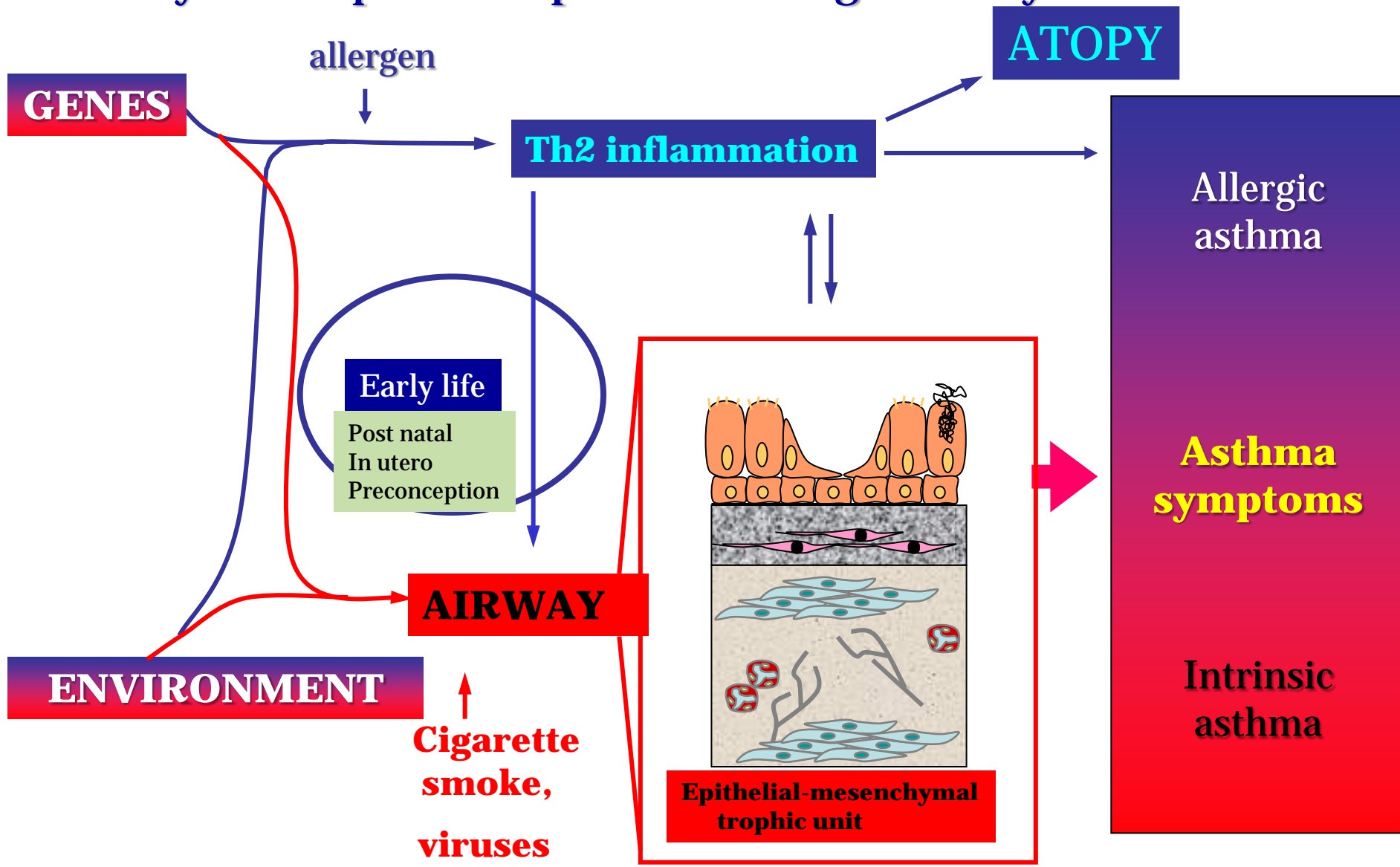
Why are the airways more susceptible in asthma?

What is the role of the epithelial-mesenchymal trophic unit in promoting allergic airway inflammation and asthma?

Why are viruses important in asthma exacerbations and pathogenesis?

What is the relationship between airways remodelling, innate immunity and allergic airways inflammation in asthma?

Working hypothesis: local tissue susceptibilities in the epithelial-mesenchymal trophic unit promote allergic airway inflammation.

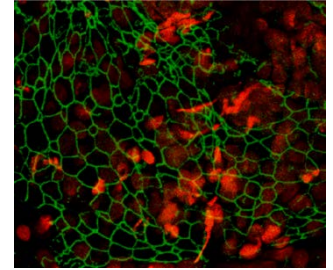


Davies DE, et al Airway remodeling in asthma: new insights. J Allergy Clin Immunol. 2003 Feb;111(2):215-25

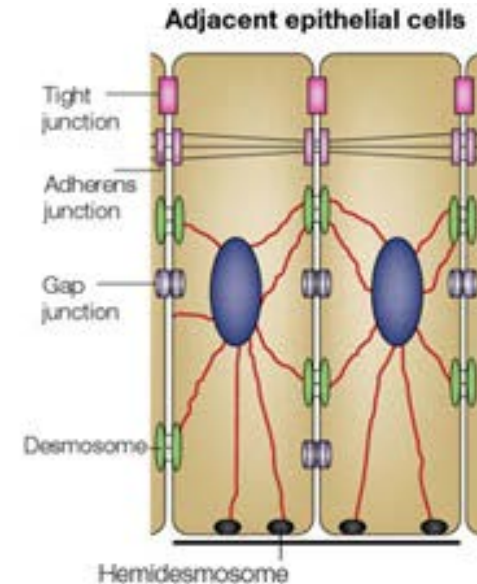
The Bronchial Epithelial Barrier

- 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**.

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

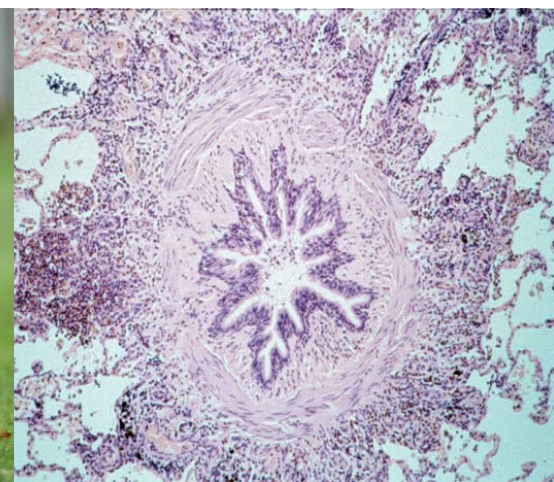
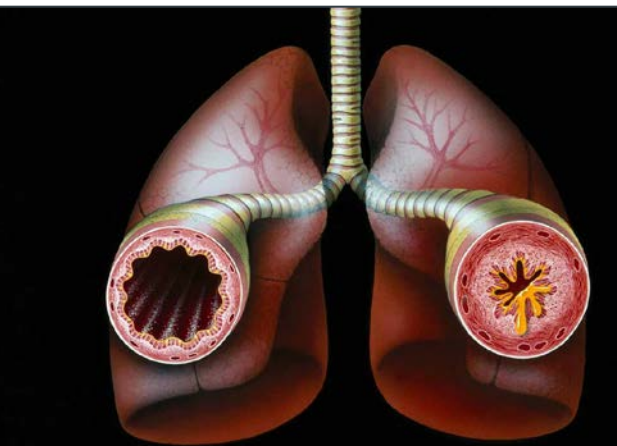


The Bronchial Epithelial Barrier in Asthma

- 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, Leino et al Plos One 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).
- **Consistent with this, in a recent clinical trial, inhaled IFN- β had a positive effect on cold-induced asthma exacerbations in severe (BTS Step 4/5) patients (10-20% of asthma patients) Djukanovic et al Am J Respir Crit Care Med. 2014 Jul 15;190(2):145-54**



Early determinants of asthma pathogenesis



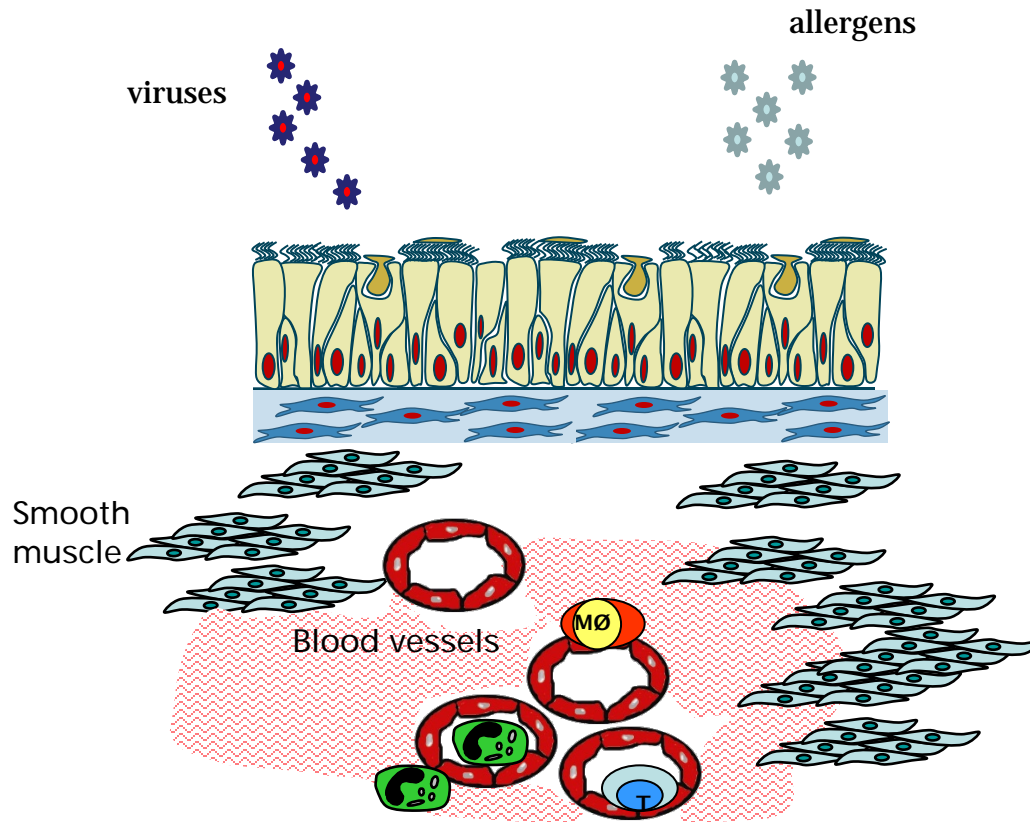
Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children.

Jackson DJ et al Am J Respir Crit Care Med. 2008; 178: 667-72.

- Define the relationship between specific viral illnesses and early childhood asthma development.
- 259 children were followed prospectively from birth to 6 years of age.
- Viral aetiologies were identified in 90% of wheezing illnesses.
- By age 3 yrs, wheezing with **RV (OR, 25.6)** was more strongly associated with asthma at age 6 years than **aeroallergen sensitization (OR, 3.4)**.
- Nearly 90% (26 of 30) of children who wheezed with RV in yr 3 had asthma at 6 yrs.

Among viral wheezing in infancy and early childhood, those caused by RV infections are the most significant predictors of the subsequent development of asthma at age 6 years in a high-risk birth cohort.

Asthma Susceptibility Genes – Links with Epithelial Immunity?



Barrier properties?

PCDH1
CDHR3

Innate immune responses?

ORMDL3-GSDML
IL33
IL1RL1
IL18R1
TSLP

TGFB2
SOCS1

Endogenous TGF β suppresses innate immunity in asthma and increases susceptibility to RV infection

Bedke N, Sammut D, Green B, Kehagia V, et al. (2012) Transforming Growth Factor-Beta Promotes Rhinovirus Replication in Bronchial Epithelial Cells by Suppressing the Innate Immune Response. PLoS ONE 7(9): e44580.
doi:10.1371/journal.pone.0044580

Bronchial epithelial cells from asthmatic donors make more TSLP and less IFN β in response to dsRNA. Uller et al Thorax. 2010 Jul;65(7):626-32.

IL-33-dependent Type 2 Inflammation During Rhinovirus-induced Asthma Exacerbations In Vivo. Jackson et al. Am J Respir Crit Care Med. First published online 28 Oct 2014 as DOI: 10.1164/rccm.201406-1039OC.

Further studies are needed to determine whether underlying differences in innate immune responses can contribute to allergic sensitisation and early life asthma susceptibility.

What is the impact of airway remodelling on the bronchial epithelium and allergic airway inflammation ?

In adults, BHR induced by methacholine increases airway remodelling in association with increased expression of epithelial TGF β , without affecting inflammation. Grainge et al N Engl J Med. 2011 May 26;364(21):2006-15.

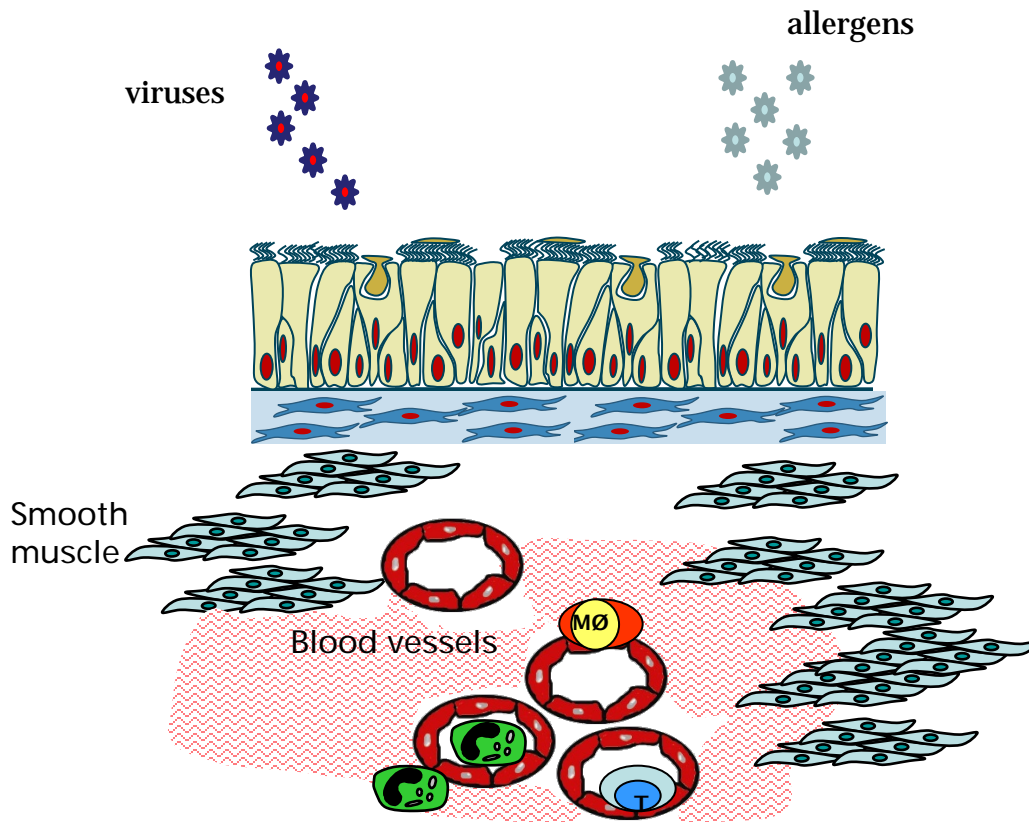
Asthmatic and normal respiratory epithelial cells respond differently to apical mechanical stress, releasing more TGF β and GM-CSF. Grainge C, Dennison P, Lau L, Davies D, Howarth P. Am J Respir Crit Care Med. 2014 Aug 15;190(4):477-80.

In a murine model of allergic airway inflammation, a GM-CSF/IL-33 pathway facilitates allergic airway responses to sub-threshold house dust mite exposure. Llop-Guevara A et al. PLoS One. 2014 Feb 14;9(2):e88714

Airway smooth muscle is increased in preschool wheezers who have asthma at school age. O'Reilly R, et al J Allergy Clin Immunol. 2013 Apr;131(4):1024-32

Do these increases in ASM augment viral associated wheeze to promote epithelial GM-CSF and IL-33 expression and allergic airways disease in early life?

Asthma Susceptibility Genes – Links with the Epithelial Mesenchymal Trophic Unit



PCDH1
CDHR3

TGFB2
SOCS1

ORMDL3-GSDML
IL33
IL1RL1
IL18R1
TSLP

ADAM33
TGFB2
GPRA (GPR154)

We need to understand how genetic polymorphism in asthma susceptibility genes affects their function to lead to development of asthma.