Decision making in lung immunity

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• Tissue complexity
• Homeostasis
• Normal processes that do not stop
Multiple factors affecting macrophage inflammatory tone
Blind folding airway macrophages: miRNA modifications

Dr Alexander Godlee
The impact of the extracellular matrix on inflammation. Lydia Sorokin
The instructive extracellular matrix of the lung: basic composition and alterations in chronic lung disease
Gerald Burgstaller, Bettina Oehrle, Michael Gerckens, Eric S. White, Herbert B. Schiller, Oliver Eickelberg.
Hyaluronan is a major constituent of the inflamed lung
Why does matrix persist?
Production versus degradation

Graphs showing fold-change over days post influenza infection for different genes and proteins.
Digestion of HA restores lung function

Hyaluronidase at d15 after influenza

Inhibits complement-dependent phagocytosis

Inter-α-Inhibitor “Naked” HMW HA

HMW HC-HA

Hyaluronidase at d15 after influenza

PenH

Methacholine (mg/ml)

Flu Naive

B d8 BAL s/n HC·HA control

HAase: N - +

free- HC

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Mechanosensing podosomes exert a protrusive force that senses environment stiffness

F-actin-rich cone-shaped structures ~600 nm height and submicron diameter,

Located at the basal face of cells, perpendicular to, and in contact with, the substratum via integrins at the podosome ring

Typical lifespan of 10 min, with an actin turnover of ~30 s
Cell death: A double edged sword in lung repair

Differential expression of TAM receptors on human macrophage subsets

Grabiec AM, Denny N, Doherty JA, ......Fowler SJ, Simpson A, Hussell T.
Diminished airway macrophage expression of the Axl receptor tyrosine kinase is associated with defective efferocytosis in asthma.
Cell death: A double edged sword in lung repair

**AMΦ**

HD

**sputum**

relative sAxl levels [a.u.]

**extracellular nucleosome [A$_{405}$]**

HD

HD

asthma

**asthma**
Apoptotic sensing by lung basal cells

Multitasking basal cells: combining stem cell and innate immune duties.
Shaykhiev R. Eur Respir J. 2015 Oct;46(4):894-7
Basal cells respond to local cues: apoptotic cells

AXL drives basal cell proliferation
Basal cell hyperplasia

Airway basal stem cells: a perspective on their roles in epithelial homeostasis and remodelling.
Epithelial macrophage cross-talk via the Glial cell line-derived neurotrophic factor family

Key roles in the control of neuron survival and differentiation.

Distant members of the TGF-β superfamily

Neurturin influences inflammatory responses and airway remodeling in different mouse asthma models.

Neuturin and its receptor in the lung

Human airway macrophages

Human Bronchial epithelial cells (Beas-2b)

Emma Connolly
Not all cells are affected equally
Most variable genes that define these clusters

IFN-response gene
Induces apoptosis
In same group as IFITM3/M2

Bind CXCR2
Recruits Mono and neuts
Where are the opportunities?

Health at different life stages
What drives change?
Do the same pathways explain immune deficits in infants?

<table>
<thead>
<tr>
<th></th>
<th>Infants (n=20)</th>
<th>Adults (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median(range)</strong></td>
<td>11 months (6-23)</td>
<td>59 years (36-78)</td>
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<tr>
<td><strong>BAL fluid instilled (mL), median</strong></td>
<td>15 (5-20)</td>
<td>50 (40-100)</td>
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<tr>
<td><strong>BAL fluid retrieval (%), median</strong></td>
<td>20 (5-40)</td>
<td>40 (20-66)</td>
</tr>
<tr>
<td><strong>AMφ yield (cells x 10^5), median</strong></td>
<td>2.9 (1.8-18)</td>
<td>2.35 (1.2-13)</td>
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Matched for sex and ethnicity
All healthy diagnosis

Dr Anu Goenka
Prof Peter Arkwright
Restoring tissue physiology to limit “inflammatory” disease

Inflamed tissues or trapped inflammatory cells?

Do our lungs become more stromal as we age?

Is there a good and bad placental environment – training pre-birth.
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