Lung Disease in Pediatrics: is it all in the Genes?

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Severe combined immunodeficiency syndrome
What CD4+ T-cells are required to prevent PCP

**TH2**
- IL-4
- IL-5
- IL-13
- IL-12
- IFN-γ
- TNF

**TH1**
- IL-2
- IFN-γ
- TNF

**Helminths, Ab response**
- STAT6
- GATA3
- T-bet

**Mycobacterium, Listeria, Viruses**
- IL-12

**APC**
- CD40
- CD40L
- CD4
- CD28
- CTLA4

**T-cell**
- B7.1
- B7.2
- MHC
- Ag
- TCR
“Effect of Antiretroviral Therapy on the Incidence of Bacterial Pneumonia in Patients with Advanced HIV Infection”

<table>
<thead>
<tr>
<th>Covariate</th>
<th>RR (crude)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 (0-50)</td>
<td>2.10</td>
<td>1.50 - 2.95</td>
<td>0.0001</td>
</tr>
<tr>
<td>CD4 (50-100)</td>
<td>1.64</td>
<td>1.05 - 2.56</td>
<td>0.03</td>
</tr>
<tr>
<td>CD4 (&gt; 100)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nucleoside analogues</td>
<td>1.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV drug usage</td>
<td>2.04</td>
<td></td>
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</tbody>
</table>
Interleukin-17A

- Homodimeric protein molecule of 32 kDa
- Produced by activated T lymphocytes, particularly CD4+, CD45RO+ T-cells
- 57% homology to Herpesvirus Saimiri ORF 13
- Induces neutrophil differentiation from CD34 progenitors in vitro and in vivo (Schwarzenberger, 1998, 2000, J. Immunol.)
IL-17 R KO mice

IL-17 is critical for Pulmonary Host Defense against Klebsiella pneumoniae

Day after *K. pneumoniae* challenge

Ye et al JEM 2001
Expression of IL-17R in murine lung

IL-17R KO  C57BL/6
Expression of IL-17R in human lung

control

Anti-IL-17R
IL-22 R Expression in murine Lung
Defective Th17 cells in Job’s Syndrome

- HIES patients
- mutations in Stat3
- recurrent infections with S aureus or C. albicans

Milner et al Nature 45
What happens in HIV/SIV infection?

Receptors for Th1, Th2, Th17, Th22 effector cytokines expressed in the lung epithelium

Arian Laurence, John J O'Shea & Wendy T Watford
Survival in AIDS related *S*. *pneumoniae* infection

Day post *S*. *pneumoniae* challenge

% survival

$n = 6$
S. pneumoniae infection elicits Th1 and Th17 responses in late stage SIV infected macaques
Low PBMC IL-22 is associated with reduced survival in AIDS related S. pneumoniae infection.
Can we measure the underlying Th profile by measuring the mucosal immunome?
Do Th17 cells require normal downstream effectors for mucosal immunity vs. tissue destruction?

• Mucociliary clearance
  - CFTR
  - ? COPD

• Neutrophils
  - CGD
  - CD18 deficiency?
Cross-sectional study of IL-23 and IL-17 in pediatric lung disease

![Graph showing cytokine levels in BAL fluid for Cystic Fibrosis and Non-CF controls]
CF lymph node culture system
T-cell recall responses to *P. aeruginosa* in CF mLN cultures

![Graph showing IL-17A and IL-17F/IL-22 production in Cystic Fibrosis (CF) and Non-CF controls, with stimulated and unstimulated conditions indicated.](image)
Critical Role of IL-23 and IL-17 in *P. aeruginosa* induced lung inflammation

WT C57BL/6  
IL-23 p19 -/-

Why do some patients with CF do worse than other?
Are there other reasons why some patients with CF with the same mutation do worse than others?

- **Modifier genes - lung disease**
  - $Tgfb1$
  - $Irfd1$ - neutrophil function

- **Modifier genes - liver disease**
  - $Tgfb1$
  - $Serpina1Z$ allele
A1-antitrypsin deficiency
Why do some patients with CF do worse than other?

• **Modifier genes – lung disease**
  - *Tgfb1*
  - *Irfd1* - neutrophil function

• **Modifier genes – liver disease**
  - *Tgfb1*
  - *Serpina1 Z* allele

• **Allergic Bronchopulmonary Aspergillosis?**
ABPA

- Asthmatics 0.5-1%
- Cystic Fibrosis 4-15%
  - Highly associated with atopy
- In CF classic ABPA can be defined as
  - 1. Acute or subacute clinical deterioration not attributable to another etiology.
  - 2. Total serum IgE concentration of 1000 IU/mL
  - 3. Immediate cutaneous reactivity to Af or in vitro demonstration of IgE antibody to Af.
  - 4. One of the following: (a) precipitins to Af or in vitro demonstration of IgG antibody to Af; or (b) new or recent abnormalities on chest radiography (infiltrates or mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy.
ABPA -a TH2 Disease?

Antonio J. and Janet Palumbo CF Center

450 CF Patients

Af negative 250

Af positive 200

35 with ABPA

165 with Af exposure
Figure 5

Luminex, Intracellular IL-4, IL-10, TGF-beta, GATA-3
Luminex, Intracellular IL-4, IL-10, TGF-beta, GATA-3
FACS for CD80, CD86, B7s1, HLA-DR, Luminex

Aspf1, Zymosan, RC, HKSC, Asp extract
CD4+ T-cells

- CD40
- CD40L
- OX40
- OX40L
- CD28
- CTLA4
- CD4
- TCR
- MHC
- B7.1
- B7.2
- Ag
- APC

IL-4
TH2
STAT 6
IL-5
IL-13

IL-4
IL-5
IL-13
Blockade of OX40L blocks Th2 cytokine production in CD4+ T-cells
Anergy versus tolerance

Mucosal Immunology advance online publication 17 February 2010.
10.1038/mi.2010.4
Af colonized CF patients have increased Tregs
 Regulatory

Foxp3+

CTLA-4

GITR

CD25

T cell precursor

Conventional T cell

Naive T cell

Naturally-arising CD4+ Treg cell

TGF-β?
Low-dose Ag?

NKT

Tr1

Th1

Th2

Th3

Foxp3+

Thymus

Periphery

IL-10 / TGF-β
CD46 ligation
VitD3 / Dex, etc.

**ABPA patients are vitamin D deficient**

<table>
<thead>
<tr>
<th></th>
<th>ABPA Positive</th>
<th>ABPA Negative</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>Vitamin D (ng/mL)</td>
<td>22.04 ± 1.999</td>
<td>36.56 ± 5.021</td>
<td>0.0201</td>
</tr>
<tr>
<td>Vitamin D w/ IL5 conc &gt;1300 pg/mL</td>
<td>18.22 ± 2.160</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Vitamin D w/ IL5 conc &lt;1300 pg/mL</td>
<td>22.45 ± 2.175</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Vitamin A (µg/dL)</td>
<td>50.93 ± 2.955</td>
<td>53.27 ± 4.188</td>
<td>0.989</td>
</tr>
<tr>
<td>Vitamin E (µg/mL)</td>
<td>9.754 ± 0.9482</td>
<td>10.13 ± 1.092</td>
<td>0.73</td>
</tr>
</tbody>
</table>
Vitamin D increases TGFβ1 expression on Tregs
CD4+ T-cells

- APC
  - CD40
  - B7.2
  - B7.1
  - MHC Ag
  - OX40L
  - Vitamin D3

- T-cell
  - CD40L
  - TCR
  - CD4
  - CD28
  - CTLA4
  - OX40

- TH2
  - IL-4
  - IL-5
  - IL-13

- TGFβ
  - Foxp3
  - IL-10
  - OX40OX40L
  - Vitamin D3
  - TGFβ
Why do some patients with CF do worse than other?

• Modifier genes – lung disease
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• Modifier genes – liver disease
  - *Tgfb1*
  - *Serpina1Z* allele

• Allergic Bronchopulmonary Aspergillosis
  - Vitamin D – alleles?
Conclusions

- Th17 cytokines regulate host defenses against extracellular pathogens in the setting of acute infection in part via regulating granulopoiesis and antimicrobial protein production
- However Th17 cytokines can exacerbate chronic lung disease when the epithelium is dysfunctional
- Vitamin D deficiency exacerbates Th2 diseases such as ABPA and asthma by inhibiting Treg development