Immune regulation in allergy and infection - the hygiene hypothesis in practice

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‘Basic Immunology Research in Allergy and Clinical Immunology”
2nd February 2014
Rising prevalence of Th2 allergy
"The Hygiene Hypothesis", 1990’s


Reduced exposure to microbial infections in affluent countries resulted in exaggerated Th2 responsiveness - and the allergy epidemic.
But... Th2-driving infections also fell in developed countries.

- TB "Th1"
- Ascaris "Th2"
- Asthma
- Eczema
- Rhinitis

... and Th1 autoimmune diseases also increased

*Childhood diabetes in United States 1900-1976*
... and Th1/Th17 Inflammatory Bowel Diseases

Data for Crohn’s Disease from Molodecky, (2011) Gastroenterology
Two worlds of Crohn’s Disease

Economou & Pappas. Inflamm Bowel Dis, 2008. 14: 709
Parallel incidence of Th1/17 Autoimmunity and Th2 Allergy

Correlation between type-1 diabetes and symptoms of asthma

*(Stene and Nafstad, *Lancet* 2001)*
Regulatory T cells suppress all effector T cell subsets

Th1/17 Inflammation, eg autoimmune disease

Th2 responses eg allergy
**Regulatory T Cells**

**Immune Responses in Healthy and Allergic Individuals Are Characterized by a Fine Balance between Allergen-specific T Regulatory 1 and T Helper 2 Cells**

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Block Autoimmunity - Enforce Self-tolerance
Maintain food tolerance
Dampen Allergies

**T-reg**

CD4

CD25

TGF-β

IL-10

Foxp3
The Revised “Hygiene Hypothesis”, from ~2003

Regulatory T cells (Tregs) can control immune pathologies of Th1 autoimmunity and Th2 allergy

- Commensal Microbiota
- Nonpathogenic Mycobacteria
- Early-life Endotoxin
- Chronic Helminths

- TLR4/CD14 alleles
- Low Endotoxin
- Early-life Antibiotics
- Acute Helminth Infection
What are Helminths?

Multicellular roundworm and flatworm parasites

- Filarial nematodes: e.g., *Brugia malayi* inhabiting human lymphatics and blood
- Schistosomes: e.g., *Schistosoma mansoni*, living in hepatic vasculature

Long-lived parasites - like Self antigens?

Induce Immune System’s own Down-Regulatory Mechanisms

<table>
<thead>
<tr>
<th>Th1</th>
<th>Th2</th>
<th>Treg</th>
</tr>
</thead>
</table>

Rick Maizels 04.02.14
### Helminth Parasites Infect >25% of the Human Population

<table>
<thead>
<tr>
<th>Species</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistosomes</td>
<td>207 million</td>
</tr>
<tr>
<td>Lymphatic Filaria (eg Brugia)</td>
<td>120 million</td>
</tr>
<tr>
<td>Trichuris trichiura</td>
<td>604 million</td>
</tr>
<tr>
<td>Ancylostoma/Necator (hookworms)</td>
<td>576 million</td>
</tr>
<tr>
<td>Ascaris lumbricoides</td>
<td>807 million</td>
</tr>
</tbody>
</table>

- Uninfected despite exposure
- Infected no pathology
- Infected pathology


Current global population ~7,000 million (Nature 20 Oct 2011)

- No vaccine exists for any human helminth infection
Regulation is dominant in helminth infection

- Resistant to infection
  - No pathology

- Infected
  - Pathology

Immunity > Regulation

Regulation > Inflammation

Inflammation > Regulation

- Th2
- ILC2
- Treg
- Th1
- Th17
IgG4 and the “Modified Th2” Phenotype

Isotype bias

Cytokine bias

IgG1 IgG2 IgG3 IgG4 IgE

Filarial Specific Antibody (µg/ml)

IFN-γ / IL-10 (pg/ml)

IFN-gamma IL-10 IL-4

IgG4 and the “Modified Th2” Phenotype

Cytokine bias

IL-4 (pg/ml)

IFN-γ / IL-10 (pg/ml)

IgG1 IgG2 IgG3 IgG4 IgE

Filarial Specific Antibody (µg/ml)
Helminth (Th2)-infected children have less allergy

Schistosome-infected children have lower allergic reactivity, and higher IL-10 responses, than uninfected

van den Biggelaar & Yazdanbakhsh, Leiden University
Anthelminthic Treatment Increases Allergy

Cumulative conversion rate of study children during 30 months.


© 2004 by the Infectious Diseases Society of America
Helminths may mitigate multiple sclerosis

Helminths may mitigate multiple sclerosis

## Helminths as Therapy?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Title</th>
<th>Conditions</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Trichuris suis</em> in Autism Spectrum Disorders</td>
<td>Asperger’s Syndrome</td>
<td>Drug: <em>Trichuris suis</em> ova</td>
</tr>
<tr>
<td>2</td>
<td><em>Trichuris suis</em> in Autism Spectrum Disorders</td>
<td>Autism</td>
<td>Drug: <em>Trichuris suis</em> ova</td>
</tr>
<tr>
<td>3</td>
<td><em>Trichuris suis</em> in Celiac Disease</td>
<td>Celiac Disease</td>
<td>Drug: <em>Trichuris suis</em> ova</td>
</tr>
<tr>
<td>4</td>
<td><em>Trichuris suis</em> in Asthma</td>
<td>Asthma</td>
<td>Drug: <em>Trichuris suis</em> ova</td>
</tr>
<tr>
<td>5</td>
<td><em>Trichuris suis</em> in Asthma and Celiac Disease</td>
<td>Asthma, Celiac Disease</td>
<td>Drug: <em>Trichuris suis</em> ova</td>
</tr>
<tr>
<td>6</td>
<td><em>Trichuris suis</em> in Allergic Rhinitis, Food Allergy, Multiple Sclerosis</td>
<td>Allergic Rhinitis, Food Allergy, Multiple Sclerosis</td>
<td>Drug: <em>Trichuris suis</em> ova</td>
</tr>
<tr>
<td>7</td>
<td><em>Trichuris suis</em> in Ulcerative Colitis, Crohn’s Disease</td>
<td>Ulcerative Colitis, Crohn’s Disease</td>
<td>Drug: <em>Trichuris suis</em> ova</td>
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<td><em>Trichuris suis</em> in Ulcerative Colitis, Crohn’s Disease</td>
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<td>9</td>
<td><em>Necator americanus</em> in Asthma and Celiac Disease</td>
<td>Asthma, Celiac Disease</td>
<td>Biological: <em>Necator americanus</em></td>
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<td>10</td>
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<td>Asthma, Celiac Disease</td>
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### Trichuris suis trials for
- Ulcerative Colitis, Crohn’s Disease
- Food Allergy, Allergic Rhinitis, Multiple Sclerosis

### Necator americanus
- hookworm trials for
- Asthma and Celiac Disease

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**But:**
- Empirical
- Higher intensity infections may be pathogenic
- Spectral response in humans not accommodated
- Neither *molecules* nor *mechanisms* understood
Model for Regulation by Parasites: *Heligmosomoides polygyrus*

- Natural parasite of mice, long-lived
- Protects mice from allergies and autoimmunity
- High throughput sequence database
**H. polygyrus**

**Tissue and luminal stages**

- **Mating**
- **Eggs**
- **Luminal Adults (d10+)**
- **Free-living infective L3**
- **Tissue-phase**
  - Day 5 L4
  - Day 3 L3
**H. polygyrus** suppresses airway allergy

*H. polygyrus* infection (200 L3)

- Day 28: 10g Allergen/Alum (i.p.) Sensitisation
- Day 42: 10g Allergen (i.t.) Airway Challenge
- Days 56-58: Sensitisation 10g Allergen (i.t.)

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Day 0 - Day 14:
- 10g Allergen/Alum (i.p.) Sensitisation
- Days 28-30: Airway Challenge

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Zaiss D et al. 2013 *Immunity* **38**: 275
"H. polygyrus" expands and activates Foxp3\(^{+}\) Tregs

\[
\begin{align*}
\text{Foxp3}^{+} \quad \text{Helios}^{+} \\
\text{CD4} \quad \text{CD25} \\
\text{Fo}\text{xp3}^{+} \quad \text{Helios}^{-} \\
\text{CD4} \quad \text{CD25}
\end{align*}
\]
Can parasite molecules replicate effects of infection?

Adult *H. polygyrus* live for 21 days in vitro, secreting macromolecules collected and concentrated as HES

*H. polygyrus* Adult Excretory-Secretory Ag (HES)
HES induces *de novo* Foxp3 expression

HES-induced Tregs suppress airway allergy

Can HES suppress *in vivo*?

HES → Treg → Foxp3 → HES

Suppresses AAl

???

Suppresses AAl
HES recapitulates suppression by live parasite infection

Day 0  Day 14  Days 28-30

OVA-Alum (i.p.) Sensitization ± HES

OVA Airway Challenge

AIRWAY INFLAMMATION

Eosinophilia

IgE

**Alternaria alternata** model of mouse airway allergy

- Common “cosmopolitan” fungus - found indoors and outdoors.
- Environmental levels associated with development and exacerbation of asthma
- Adjuvant-free airway sensitization in mouse models
HES blocks both innate and adaptive allergic responses

Alternaria alternata intranasal ± OVA ± HES

Early Innate (Ag-independent) Eosinophilia

Late Adaptive (Ag- and T-cell-dependent) Eosinophilia

McSorley HJ et al 2014 Mucosal Immunology
HES suppresses Innate Lymphoid Cell responses

Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity

McSorley HJ et al 2014 Mucosal Immunology
IL-33 not IL-25 is central to allergy and HES suppression

IL-25R-deficient mice (McKenzie)

Exogenous IL-33

McSorley, Mucosal Immunology in press
Parasite blockade of IL-33 response

- Epithelial Cells
- HES
- IL-33
- Innate Lymphoid Cell (ILC)
- Eosinophils
- Goblet Cells
- Mucus Production
- IL-5
- IL-13
- Allergenic Recall Response
  - Alternately-activated macrophage
  - Th2
Blocking both Innate and Adaptive Pathways of Allergy

Dampens Allergic (TH2) Effectors

Prevents Allergic (TH2/ILC2) Sensitization

Soluble Immunomodulators

Airway Allergy
Maizels Lab Edinburgh

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