Microbiome and Respiratory Disease

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HLA-B27 Associated Inflammation

• Humans who have inherited the human class I major histocompatibility allele HLA-B27 have a markedly increased risk of developing the multi-organ system inflammatory diseases of joints (spondyloarthropathies)

• Transgenic rats expressing HLA-B27 and human β₂m develop spontaneous inflammatory disease involving the gastrointestinal tract, peripheral and vertebral joints, male genital tract, skin, nails, and heart
HLA-B27 Associated Inflammation

- B27 transgenic rats raised in a germfree environment do not develop inflammatory intestinal or peripheral joint disease, whereas the skin and genital inflammatory lesions are unaffected by the germfree state.
Regulation of Inflammation
Regulation of Inflammation

Inflammatory

Anti-inflammatory
Regulation of Inflammation

Dysbiosis

Inflammatory

Anti-inflammatory
### Epidemiologic Associations between Fecal Microbiota Composition and Allergies

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Allergies</th>
<th>Experiments</th>
<th>Microflora Associations with Allergic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>27-35 Estonia + Sweden</td>
<td>2 yr</td>
<td>AD (FA)</td>
<td>clinical and SPT</td>
</tr>
<tr>
<td>25-47 Sweden</td>
<td>12 mo</td>
<td>AD, asthma, FA</td>
<td>clinical and SPT</td>
</tr>
<tr>
<td>44 (18) Estonia + Sweden</td>
<td>0-2 yr</td>
<td>AD (FA)</td>
<td>clinical and/or SPT</td>
</tr>
<tr>
<td>4-6 NR</td>
<td>2-7 mo</td>
<td>AD and FA</td>
<td>clinical</td>
</tr>
<tr>
<td>76 (22) Finland</td>
<td>0-12 mo</td>
<td>atopy (+/- AD/FA)</td>
<td>SPT (clinical)</td>
</tr>
<tr>
<td>27-10 Finland</td>
<td>0-14 mo</td>
<td>AD (FA)</td>
<td>clinical and SPT</td>
</tr>
<tr>
<td>7-6 NR</td>
<td>2-7 mo</td>
<td>AD</td>
<td>clinical and SPT</td>
</tr>
<tr>
<td>10-10 UK</td>
<td>12 mo</td>
<td>atopic wheeze</td>
<td>clinical and SPT</td>
</tr>
<tr>
<td>30-68 Japan</td>
<td>&lt; 20 yr</td>
<td>AD</td>
<td>clinical</td>
</tr>
<tr>
<td>33-33 (8-8) UK</td>
<td>3-5 yr</td>
<td>atopic wheeze (AD)</td>
<td>clinical and SPT</td>
</tr>
<tr>
<td>19-19 Estonia</td>
<td>5 yr</td>
<td>AD, asthma, allergic rhinitis</td>
<td>clinical and SPT and/or IgE</td>
</tr>
<tr>
<td>21-28 Singapore</td>
<td>~3 yr</td>
<td>AD</td>
<td>clinical</td>
</tr>
</tbody>
</table>
# Epidemiologic Associations between Antibiotic Use and Allergies

<table>
<thead>
<tr>
<th>Year</th>
<th>Design a</th>
<th>Number</th>
<th>Residence</th>
<th>Description</th>
<th>Evaluation Criteria b</th>
<th>Data Collection c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>Retro (PB-BC)</td>
<td>1934</td>
<td>UK</td>
<td>General</td>
<td>&lt; 2 yr</td>
<td>MR</td>
</tr>
<tr>
<td>1990</td>
<td>Retro (PB)</td>
<td>5067+</td>
<td>Germany</td>
<td>General</td>
<td>&lt; 3 yr</td>
<td>PR</td>
</tr>
<tr>
<td>1990</td>
<td>Retro (CSS)</td>
<td>456</td>
<td>New Zealand</td>
<td>Anthroposophic (RS)</td>
<td>&lt; 1 yr</td>
<td>PR</td>
</tr>
<tr>
<td>2000</td>
<td>Retro (PB)</td>
<td>742</td>
<td>Belgium</td>
<td>General</td>
<td>&lt; 1 yr</td>
<td>PR</td>
</tr>
<tr>
<td>2001</td>
<td>Pro (PB-BC)</td>
<td>939</td>
<td>Germany</td>
<td>General (38% atopy risk factors)</td>
<td>&lt; 3 yr</td>
<td>PR</td>
</tr>
<tr>
<td>2001</td>
<td>Retro (PB)</td>
<td>2512</td>
<td>Germany</td>
<td>General</td>
<td>any</td>
<td>PR</td>
</tr>
<tr>
<td>2002</td>
<td>Pro (FH)</td>
<td>498</td>
<td>US</td>
<td>FH of atopy</td>
<td>&lt; 1 yr</td>
<td>PR</td>
</tr>
<tr>
<td>2002</td>
<td>Pro (PB-BC)</td>
<td>29,238</td>
<td>UK</td>
<td>General</td>
<td>&lt; 1 yr</td>
<td>MR</td>
</tr>
<tr>
<td>2003</td>
<td>Retro (C-C)</td>
<td>7098-7098</td>
<td>UK</td>
<td>hayfever-control</td>
<td>&lt; 1 yr</td>
<td>MR</td>
</tr>
<tr>
<td>2003</td>
<td>Pro (PB)</td>
<td>4408</td>
<td>US</td>
<td>General</td>
<td>&lt; 1 yr</td>
<td>MR</td>
</tr>
<tr>
<td>2004</td>
<td>Retro (CSS)</td>
<td>1584</td>
<td>New Zealand</td>
<td>childhood infections</td>
<td>&lt; 1 yr</td>
<td>PR</td>
</tr>
<tr>
<td>2004</td>
<td>Retro (PB)</td>
<td>746</td>
<td>UK</td>
<td>General</td>
<td>&lt; 5 yr</td>
<td>PR</td>
</tr>
<tr>
<td>2005</td>
<td>Retro (PB)</td>
<td>26,400</td>
<td>Korea</td>
<td>General</td>
<td>&lt; 1 yr</td>
<td>PR</td>
</tr>
<tr>
<td>2005</td>
<td>Pro (PB-BC)</td>
<td>448</td>
<td>US</td>
<td>General</td>
<td>&lt; 6 mo</td>
<td>MR</td>
</tr>
</tbody>
</table>
Effect of Microbiota Disruption on the Allergic Response to Mold Spores following GI Microbiota Disruption

IL-5 (pg/ml)

0
500
1000
1500
2000

Microbiota Disruption
Mold Spore Challenge

X                     X

X                     X

Lung Eosinophils (x 10^5)

0
10
20
30
40
50

Microbiota Disruption
Mold Spore Challenge

X                     X

X                     X

IL-13 (pg/ml)

0
500
1000
1500
2000
2500
3000

Microbiota Disruption
Mold Spore Challenge

X                     X

X                     X

Mast Cells (per 15 MPF)

0
10
20
30
40
50
60
70

Microbiota Disruption
Mold Spore Challenge

X                     X

X                     X

MPF=20x field

Noverr MC et al.
Effect of Microbiota Disruption on Mucus Production Following Mold Spore Challenge

PAS Stain (Goblet Cell Metaplasia)

Effect of Microbiota Disruption on the Allergic Response to Mold Spores following GI Microbiota Disruption

- CD4 T cell dependent
- IL-13 dependent
- Can be induced in C57BL/6 and Balb/c mice
- Can be induced to both OVA and Aspergillus spores

The Human Microbiome
Gut-Lung Axis of Immunoregulation

Antigen

Pulmonary Immune System

Outcome of Pulmonary Challenge
Gut-Lung Axis of Immunoregulation

Antigen

Pulmonary Immune System

Outcome of Pulmonary Challenge
Gut-Lung Axis of Immunoregulation

Antigen

Pulmonary Immune System

Outcome of Pulmonary Challenge

Gut Immune System
Gut-Lung Axis of Immunoregulation

Outcome of Pulmonary Challenge
Gut-Lung Axis of Immuno-regulation

Antigen

Pulmonary Immune System

Outcome of Pulmonary Challenge

Antigen

Gut Immune System

Microbiota

Immune Regulation
The Human Microbiome
Regulation of Inflammation

GI Tract

Airways?

Dysbiosis

Inflammatory

Anti-inflammatory
The National Institutes of Health
Human Microbiome Project

Overview

Within the body of a healthy adult, microbial cells are estimated to outnumber human cells by a factor of ten to one. These communities, however, remain largely unstudied, leaving almost entirely unknown their influence upon human development, physiology, immunity, and nutrition. To take advantage of recent technological advances and to develop new ones, the NIH Roadmap has initiated the Human Microbiome Project (HMP) with the mission of generating resources enabling comprehensive characterization of the human microbiota and analysis of its role in human health and disease.

Traditional microbiology has focused on the study of individual species as isolated units. However, many, if not most, have never been successfully isolated as viable specimens for analysis, presumably because their growth is dependent upon a specific microenvironment that has not been, or cannot be, reproduced experimentally. Among those species that have been isolated, analyses of genetic makeup, gene expression patterns, and metabolic physiology have rarely extended to inter-species interactions or microbe-host interactions. Advances in DNA sequencing technologies have created a new field of research, called metagenomics, allowing comprehensive examination of microbial communities, even those comprised of uncultivable organisms. Instead of examining the genome of an individual bacterial strain that has been grown in a laboratory, the metagenomic approach allows analysis of genetic material derived from complete microbial communities harvested from natural environments. In the HMP, this method will

Nasal
Oral
Skin
Gastrointestinal
Urogenital
The Microbiome of the Lungs

---“Healthy” Smokers---  ---COPD---  Non-Smokers

2011;6(2):e16384.
Analysis of the Human Pulmonary Microbiome in Bronchoalveolar Lavage Fluid

Heterogeneity in the Distribution of the Pulmonary Microbiome during Disease

Disordered microbial communities in asthmatic airways


The bronchial tree was not sterile....the results show the bronchial tree to contain a characteristic microbiota, and suggest that this microbiota is disturbed in asthmatic airways.
A persistent and diverse airway microbiota present during chronic obstructive pulmonary disease exacerbations


PhyloChip analysis revealed the presence of over 1,200 bacterial taxa representing 140 distinct families, many previously undetected in airway diseases
Characterization of bacterial community diversity in cystic fibrosis lung infections by use of 16s ribosomal DNA terminal restriction fragment length polymorphism profiling

Rogers GB, Carroll MP, Serisier DJ, Hockey PM, Jones G, Bruce KD.

We used terminal restriction fragment length polymorphism profiling and 16S rRNA clone data to characterize, without prior cultivation, the bacterial community in sputa from adult CF patients..... reveals the enormous complexity of bacteria within the CF lung.
Effect of Antibiotics, Medications and Diet on the Microbiota

Antibiotics

Dietary Phenols

Microbiota

Probiotics

Fiber, sugar, starch

Host Mucosal Cells

Medications
HLA-B27 Associated Inflammation

- Transgenic rats expressing HLA-B27 and human $\beta_2$m develop spontaneous inflammatory disease involving the gastrointestinal tract, peripheral and vertebral joints, male genital tract, skin, nails, and heart.

- B27 transgenic rats raised in a germfree environment do not develop inflammatory intestinal or peripheral joint disease, whereas the skin and genital inflammatory lesions are unaffected by the germfree state.
HLA-B27 Associated Inflammation

- Administered 7.6% lyophilized apples obtained from two cultivars to HLA-B27 transgenic rats
  - Golden Delicious (low polyphenol)
  - Marie Ménard (high polyphenol)

- The administration of Marie Ménard apples, rich in polyphenols and used at present only in the manufacturing of cider, ameliorated colon inflammation

University of Florence, Florence, Italy
The $ponsor$

- The National Institute of Allergy and Infectious Diseases (NIAID)
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    - Abbott Nutrition
  - University of Michigan Department of Internal Medicine
  - Michigan Institute for Clinical Health Research (MICHR)

Thank you!
The Research Group

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