Atopy: The Common and the Rare Allergies in the Genomic Era

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Pathogenesis of Allergic Disease

Genetic Susceptibility
- Adaptive Immunity
- Innate Immunity
- Intestinal and skin barrier

Environmental Triggers
- Hygiene hypothesis
- Host microbiome
- Vitamin D deficiency
- Timing of food introduction
Tolerance versus Allergic Inflammation

Skin  Airways  Gastrointestinal (GI) Tract
Development of Immunologic Tolerance

Food Antigens

Gut lumen

Small Intestinal Lamina Propria

CX3CR1⁺ MΦ

CD103⁺ DC

Mesenteric Lymph Node

Present Ag

Naïve CD4⁺

Antigen-specific Treg

+ TGFβ, retinoic acid

Th2
Development of Immunologic Tolerance

Food Antigens → Gut lumen → Small Intestinal Lamina Propria → Mesenteric Lymph Node

- CX3CR1⁺ MΦ
- CD103⁺ DC
- Naïve CD4⁺ T cells
- Antigen-specific Treg
- Antigen-presenting cells (Ags) + TGFβ, retinoic acid

Present Ag → Naïve CD4⁺ + TGFβ, retinoic acid → Antigen-specific Treg
Loeys-Dietz Syndrome (LDS)

- Caused by mutations
  - *TGFBR1* (Type I)
  - *TGFBR2* (Type II)

- Triad of:
  - Hypertelorism
  - Cleft palate/bifid uvula
  - Arterial tortuosity, aneurysm, and dissection

# Increased Prevalence of Allergic Disease in LDS

<table>
<thead>
<tr>
<th>Condition</th>
<th>LDS</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eczema</td>
<td>32%</td>
<td>10-20% (children), 1-3% (adult)</td>
</tr>
<tr>
<td>Seasonal Allergies</td>
<td>41%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Asthma</td>
<td>38%</td>
<td>9%</td>
</tr>
<tr>
<td>Food Allergy</td>
<td>24%</td>
<td>6% (children), 3-4% (adult)</td>
</tr>
<tr>
<td>Eosinophilic Esophagitis (EoE)</td>
<td>10%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

Frischmeyer-Guerrerio PA et al. Sci Transl Med 2013; 5:195
Elevated Total Serum IgE Levels and Peripheral Eosinophilia in LDS Patients

Increased Tregs in Peripheral Blood of LDS Patients

LDS Tregs Promote Th2 Inflammation

- Increased frequency of Treg subsets that express IL-13 (Th2) in LDS and nonsyndromic allergic disease
- No difference in expression of IFNγ, a Th1 cytokine

Alterations in TGFβ signaling predispose to allergic disease

Development of Immunologic Tolerance

*CX3CR1*^+^ MΦ

CD103^+^ DC

Present Ag

Naïve CD4^+^ + TGFβ, retinoic acid

Antigen-specific Treg

Th2
Germ Free Mice Exhibit Th2 Skewing

- Increased total serum IgE levels

- Fail to develop oral tolerance and exhibit increased anaphylactic responses in murine model of food allergy

- Exhibit exaggerated airway inflammation following allergen exposure compared to SPF mice

- Colonization of germ free mice with a mixed flora prevents Th2 skewing and allergic predisposition

Gollwitzer ES et al. 2014; Nat Med 20: 642
Stefka AT et al. 2014; Proc Natl Acad Sci USA 111: 13145
Role of Diet in Predisposition to Allergic Disease

High Fiber Diet

Low Fiber “Westernized” Diet
Low Fiber Diet Increases Susceptibility to Allergic Inflammation

Low-Fiber Diet: 0.3% fiber
Control: 4% fiber

Trompette A et al. 2014; Nat Med 20(2): 159
Low Fiber Diet Alters the Composition of the Intestinal Microbiome

Low-Fiber Diet: 0.3% fiber
Control: 4% fiber

Trompette A et al. 2014; Nat Med 20(2): 159
Short Chain Fatty Acids (SCFA) Promote Tolerance

<table>
<thead>
<tr>
<th>Propionate (SCFA)</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H&amp;E staining</strong></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>Propionate</td>
</tr>
</tbody>
</table>

Protective Effect of SCFAs due to:
- Enhanced hematopoiesis of DC precursors in the bone marrow that exhibited a reduced ability to activate Th2 effector cells in the lung

Trompette A et al. 2014; Nat Med 20(2): 159
Evidence for a Role of the Microbiome in Tolerance to Allergens in Humans

Epidemiologic Evidence: Risk factors for allergic disease include:

- pre- and perinatal antibiotic exposure
- delivery by C-section
- urban (vs. farm) living
- formula feeding
- no pet (dog)
- increased urinary levels of antimicrobial agents (triclosan)
Canadian Healthy Infant Longitudinal (CHILD) Study

- Multi-center, longitudinal, prospective general birth cohort study
- Followed 319 infants from birth through 5 years of age
- Subjects were grouped into 4 clinical phenotypes:
  - Atopy and wheeze (AW group): 20 fold higher risk of developing asthma by age 3y
  - Atopy only
  - Wheeze only
  - Controls
    - Stool was collected at 3 mo and 1 year

Arietta, M-C et al. 2015; Sci Transl Med 7(307): 307ra152
Gut Microbial Composition by Clinical Phenotype

Arietta, M-C et al. 2015; Sci Transl Med 7(307): 307ra152
Composition of the intestinal microbiome very early in life may be associated with the risk of developing allergic disease

Arietta, M-C et al. 2015; Sci Transl Med 7(307): 307ra152
Probiotics: Role in Allergic Disease

Definition: “Living microorganisms which, upon ingestion in certain numbers, exert health benefits beyond general nutrition”

Most probiotics used clinically are similar to bacteria that naturally colonize the human gut, including Bifidobacterium and Lactobacillus
Probiotics: Role in Allergic Disease

Proposed mechanism(s) of action:

- Promote Treg production by enhancing production of IL10 and/or TGFβ
- Promote production of SCFA and other favorable metabolites
- Repair gut barrier function and enhance IgA production
Probiotics: Can They Prevent Allergic Disease?

No study where probiotics have been administered postnatally have shown any benefit for the treatment or prevention of any form of allergic disease.

Combination of prenatal and postnatal supplementation may modestly reduce eczema.

Not sufficient data to recommend routine use.

West CE et al. 2015; JACI 135: 3
Emerging Therapies to Induce Favorable Changes in Gut Microbiota

Use different strains of bacteria (Clostridia, Bacteroides species) that are stronger producers of SCFA

Fecal Microbiota Transplant (FMT):

- Given nasogastrically or via colonoscopy
- Effective in treating antibiotic-resistant *C. difficile* in a randomized controlled trial
- No published trials in allergic disease
- More information regarding long-term effects and safety is needed

West CE et al. 2015; JACI 135: 3
“Window of Opportunity”

McCoy KD et al. 2015; Clin Immunol 159: 170
Infant Feeding Practices

• 2000: AAP recommended waiting until 3 yo to introduce peanut in infants at high risk for allergic disease

• 2008: AAP retracted the recommendation
Prevalence of Peanut Allergy

• 0.4% in 1997
• 1.4% in 2008
• >2% in 2010

• Leading cause of anaphylaxis and death related to food allergy in US
Is Early Introduction of Foods Better?

– 2008 DuToit et al: prevalence of peanut allergy 10 times higher among Jewish children in London compared to Jewish children in Israel

– 2010 Katz et al: prevalence of IgE-mediated cow’s milk allergy was 0.05% in those started on cow’s milk formula within the first 14 days vs. 1.75% among those started between 105-194 days of age

– 2010 Koplin et al: compared to introduction of egg at 4-6 months, Odds Ratio of developing egg allergy was 1.6 if introduced between 10-12 months and 3.4 if after 12 months

Du Toit Get al. 2008; JACI 122: 984
Katz Y et al. 2010; JACI 126:77
Koplin JJ et al. 2010; JACI 126:807
Learning Early About Peanut Allergy (LEAP) Study

• Does early introduction of peanut into the diet prevent the development of peanut allergy?

• Randomized open label controlled trial at a single site in the United Kingdom

• Enrolled infants 4-11 mo of age (median 7.8 mo ± 1.7mo) who had severe eczema, egg allergy, or both

Du Toit G et al. 2015; NEJM 372: 803
LEAP study

• Divided infants into 2 groups:
  – Positive SPT to peanut (1-4 mm wheal); n=98
  – Negative SPT to peanut; n=542

• Randomly Assigned to:
  Peanut Consumption vs. Avoidance

Bamba

Du Toit G et al. 2015; NEJM 372: 803
Primary Outcome: Peanut Allergy at Age 5yo

A Intention-to-Treat Analysis

- **SPT-Negative Cohort (N=530)**
  - Avoidance Group: 13.7%
  - Consumption Group: 1.9%
  - P < 0.001

- **SPT-Positive Cohort (N=98)**
  - Avoidance Group: 35.3%
  - Consumption Group: 10.6%
  - P = 0.004

- **Both Cohorts (N=628)**
  - Avoidance Group: 17.2%
  - Consumption Group: 3.2%
  - P < 0.001

B Per-Protocol Analysis

- **SPT-Negative Cohort (N=500)**
  - Avoidance Group: 13.9%
  - Consumption Group: 0.4%
  - P < 0.001

- **SPT-Positive Cohort (N=89)**
  - Avoidance Group: 34.0%
  - Consumption Group: 0.0%
  - P < 0.001

- **Both Cohorts (N=589)**
  - Avoidance Group: 17.3%
  - Consumption Group: 0.3%
  - P < 0.001

Du Toit G et al. 2015; NEJM 372: 803
Immunologic Outcomes

Du Toit G et al. 2015; NEJM 372: 803
Immunologic Outcomes

IgG (spec. IgG4) may inhibit allergic responses by:

- Competing with IgE for binding to allergen
- Activating inhibitory Fcγ receptors on mast cells and basophils

Early oral introduction of peanut may prevent allergy in high-risk infants

Du Toit G et al. 2015; NEJM 372: 803
Allergen Immunotherapy

- Disease Activity
- Allergen Dose
- Weekly
- Every 2 weeks
Immunotherapy for Allergic Disease

Induction of allergen-specific Tregs following immunotherapy

Allergens

Treg

Suppression of other Th2 functions
- Mucus production (by IL-9, IL-13)
- Tissue homing of Th2 cells (by IL-4, IL-13)

IL-10, TGF-β

IL-3
IL-4
IL-5

Th2

IL-4
IL-13

IgE production

Early desensitization of effector cells

IgG4 production from B cells

Immunotherapy Timeline

“Allergy shots” to Grass pollen

1911

Blocking Abs

IgE

T Regs

1940

1966

1969

1980

1984

1988

1992

1998

2005

2009

WHO: SLIT “viable alternative” for aeroallergens

Case Reports of Oral Immunotherapy for Food Allergy

Trial peanut “shots”

Well Designed Food Immunotherapy Trials

Hazelnut

Egg SLIT

OIT

Milk OIT

Peanut OIT

Immunotherapy for Allergic Disease

Subcutaneous ("Allergy Shots") (SCIT)

Sublingual (SLIT)

Oral (OIT)
Oral Immunotherapy (OIT) for Food Allergy

- Best studied for the most common food allergens: milk, egg, and peanut
- Side effects are extremely common, mostly mild
- Most patients experience a significant increase in the amount of the food they can eat before having a reaction
- Only a minority of children achieve “lasting tolerance”
Allergic disease results from a defect in the establishment or maintenance of tolerance to innocuous environmental antigens.

Several early life events that alter the intestinal microbiota may influence an individual’s predisposition to allergic disease.

Allergen immunotherapy is often an effective treatment for allergic disease.