Atopy: the Common and the Rare--Allergies in the Genomic Era
Outline

• What is an allergy?
• How do they happen and how can we treat them?
• Why do we have them?
• Why are they on the increase?
• How do genetics contribute to allergy?
  – Examples: Eczema, monogenic diseases of allergy
## What are allergies?

<table>
<thead>
<tr>
<th>Immediate allergies</th>
<th>“chronic” allergies</th>
<th>Not allergies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anaphylaxis</td>
<td>• Eosinophilic esophagitis</td>
<td>• Lactose intolerance</td>
</tr>
<tr>
<td>• Breaking out into hives within 4 hours of food or drug</td>
<td>• Protein proctitis/proctocolitis (blood in the diaper)</td>
<td>• Celiac disease</td>
</tr>
<tr>
<td>• Hay Fever (allergic rhin conjunctivitis)</td>
<td>• Eczema</td>
<td>• Most Drug reactions</td>
</tr>
<tr>
<td>• Many types of asthma attacks</td>
<td>• Allergic contact dermatitis*</td>
<td>• Reflux/Heartburn</td>
</tr>
<tr>
<td>• The oral allergy syndrome</td>
<td>• Lung, esophagus, and nasal mucosal remodeling</td>
<td>• Joint pain</td>
</tr>
<tr>
<td>• Vomiting soon after eating a food*</td>
<td></td>
<td>• <strong>Over half of reported food allergies!!!</strong></td>
</tr>
</tbody>
</table>
Other types of allergic symptoms

• Hives—triggered or not
• Chronic itching
• Skin flushing (although allergies can cause a lot of the other kind too)
• Certain types of abdominal pain
• Drop in blood pressure
What’s the best way to know I’m allergic to something?

• I notice hives, itching, throat closure or loss of blood pressure within 4 hours of being exposed, usually by eating a food or drug, or getting it by IV

• I get a runny nose and wheeze at the same time of year every year, or in the same house that I visit every time (exception: in-laws’ place)
What’s the best way to get me skeptical about whether I have an allergy?

• A skin or blood test I receive that someone drew along with 300 other tests “just to check”, says I’m allergic to milk. I read it while eating pizza and yogurt.
“Allergy Tests”

- Skin prick or patch
- Blood IgE
  - RAST
  - Validated vs. unvalidated
- Challenge
- Pulmonary function
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How do allergies happen?
IgE– a major player in acute “allergy attacks”

- IgM
- IgG
- IgA
- IgE

Hives
Itchy skin
Sneezing
Wheezing
Runny nose
Vomiting
Anaphylaxis

Leaky/dilated blood vessels

Antigenic tolerance
IgE Blockade
Anitihistamines
Vasoconstrictors
Mast cell stabilizers
Corticosteroids

Acute Allergy vs. Allergic Inflammation

(Kay NEJM 2001)
Atopic dermatitis: an example of chronic allergic inflammation
But I’ve taken antihistamines, steroids and Xolair and I still itch

• We don’t know everything, regardless of what we say
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Triggering “type 2” responses

Pulendran et al. Science 2012
Why do we have allergies?
Keeping bee stings at bay?

Development of venom-specific IgE ( sư )

IgE-dependent increased resistance

Sublethal amount of honeybee venom

Wild-type mouse

Type 2 immune response

Potentially lethal amount of honeybee venom

Mouse lacking venom-specific IgE ( sư ), or the α or γ chain of FcεRI ( FcεRIαγ )

High susceptibility

Immunity 2013
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Why are allergies worse nowadays?

• The hygiene hypothesis
  – We avoid bugs too much
• Delayed introduction of solid foods
  – We avoid foods too much
• Western lifestyle
  – We are exposed to the wrong bugs, the wrong foods, and the wrong chemicals
  – “Doctor, Xanax is the most wonderful antihistamine I have ever taken.”
Getting up here and speaking is worse than electric shock

Prior to speech, pretreatment with mast cell stabilizer (cromolyn)

Vanuytsel et al, Gut 2014
The microbiome and allergy

A microbiota signature associated with experimental food allergy promotes allergic sensitization and anaphylaxis

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Background: Commensal microbiota play a critical role in maintaining oral tolerance. The effect of food allergy on the gut microbial ecology remains unknown.

Objective: We sought to establish the composition of the gut microbiota in experimental food allergy and its role in disease pathogenesis.

Methods: Food allergy–prone mice with a gain-of-function mutation in the IL-4 receptor α chain (Il4raF709) and wild-type (WT) control animals were subjected to oral sensitization with chicken egg ovalbumin (OVA). Enforced tolerance was achieved by using allergen-specific regulatory T (Treg) cells. Community structure analysis of gut microbiota was performed by using a high-density 16S rDNA oligonucleotide microarrays (PhyloChip) and massively parallel pyrosequencing of 16S rDNA amplicons.

Results: OVA-sensitized Il4raF709 mice exhibited a specific microbiota signature characterized by coordinate changes in the abundance of taxa of several bacterial families, including the Lachnospiraceae, Lactobacillaceae, Rikenellaceae, and Porphyromonadaceae. This signature was not shared by similarly sensitized WT mice, which did not exhibit an OVA-induced allergic response. Treatment of OVA-sensitized Il4raF709 mice with OVA-specific Treg cells led to a distinct tolerance–associated signature coincident with the suppression of the allergic response. The microbiota of allergen-sensitized Il4raF709 mice differentially promoted OVA-specific IgE responses.

Conclusion: Mice with food allergy exhibit a specific microbiota signature capable of transmitting disease susceptibility and subject to reprogramming by immune tolerance. Disease-associated microbiota may thus play a pathogenic role in food allergy. (J Allergy Clin Immunol 2013;131:201-12.)

Key words: Food allergy, microbiome, microbio T cells, tolerance, anaphylaxis, IgE, 16S rDNA, IL-4

It is unquestionable that food allergy has become a problem in developed countries, where the prevalence is 6% among children and 3% among adults.1,2 Likewise, diseases, food allergies have a strong genetic component. In the last decades, particularly in affluent societies, lifestyle-associated environmental factors acting...
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Genetics and allergy

• Are allergies genetic disorders whose penetrance increase over time?
• Elevated pH (from soap, detergents, etc.) increases protease activity

Cork, et al JACI 2006
Comel-Netherton Syndrome
A physical barrier defect

• Congenital ichthyosis and allergen-specific atopic diathesis

• Caused by mutations in SPINK5—gene encoding LEKTI a protease in the corneodesmosome

Renner et al JACI 2009
Filaggrin mutations increase risk for typical AD—importance of barrier function in AD pathogenesis

<table>
<thead>
<tr>
<th>Combined genotype</th>
<th>Odds ratio (random) (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marenholz 2006$^w12$</td>
<td>3.73 (1.98 to 7.02)</td>
<td>3.73 (1.98 to 7.02)</td>
</tr>
<tr>
<td>Palmer (Denmark) 2006$^w1$</td>
<td>2.49 (1.26 to 4.93)</td>
<td>2.49 (1.26 to 4.93)</td>
</tr>
<tr>
<td>Palmer (Ireland) 2006$^w1$</td>
<td>13.40 (6.20 to 27.50)</td>
<td>13.40 (6.20 to 27.50)</td>
</tr>
<tr>
<td>Barker 2007$^w10$</td>
<td>7.70 (5.30 to 10.90)</td>
<td>7.70 (5.30 to 10.90)</td>
</tr>
<tr>
<td>Leibaek 2007$^w9$</td>
<td>3.50 (1.21 to 9.99)</td>
<td>3.50 (1.21 to 9.99)</td>
</tr>
<tr>
<td>Sandilands 2007$^w3$</td>
<td>10.02 (6.75 to 14.89)</td>
<td>10.02 (6.75 to 14.89)</td>
</tr>
<tr>
<td>Stemmler 2007$^w17$</td>
<td>4.18 (2.60 to 6.73)</td>
<td>4.18 (2.60 to 6.73)</td>
</tr>
<tr>
<td>Weidinger 2007$^w16$</td>
<td>4.17 (2.30 to 7.59)</td>
<td>4.17 (2.30 to 7.59)</td>
</tr>
<tr>
<td>Brown 2008$^w19$</td>
<td>6.46 (4.47 to 9.32)</td>
<td>6.46 (4.47 to 9.32)</td>
</tr>
<tr>
<td>Weidinger 2008$^w23$</td>
<td>4.56 (3.08 to 6.74)</td>
<td>4.56 (3.08 to 6.74)</td>
</tr>
<tr>
<td>Brown 2008$^w22$</td>
<td>1.53 (0.98 to 2.37)</td>
<td>1.53 (0.98 to 2.37)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>4.78 (3.31 to 6.92)</td>
<td>4.78 (3.31 to 6.92)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: df(Q)=10, P=0, z=8.31

van den Oord, R. A H M et al. BMJ 2009;339:b2433
Protecting the barrier wraps
Get ST pics
Eczema Herpeticum

Journal of Allergy and Clinical Immunology
Available online 3 September 2015
In Press, Corrected Proof — Note to users

Targeted deep sequencing identifies rare loss-of-function variants in IFNGR1 for risk of atopic dermatitis complicated by eczema herpeticum

Li Gao, MD, PhD*, Lianghua Bin, PhD†, Nicholas M. Raafaels, MS*, Lili Huang, MS*, Joseph Potee, MS*, Ingo Ruczinski, PhD*, Terri H. Beatty, PhD†, Amy S. Paller, MD*, Lynda C. Schneider, MD*, Rich Gallo, MD, PhD†, Jon M. Hanifin, MD*, Lisa A. Beck, MD†, Raif S. Geha, MD†, Rasika A. Mathias, ScD*, Kathleen C. Barnes, PhD*.  |  *†‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †‡ †}]
## Monogenic diseases of atopy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Causative Gene</th>
<th>Primary pathologic mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPEX</td>
<td>FOXP3</td>
<td>Treg failure</td>
</tr>
<tr>
<td>AD-HIES</td>
<td>STAT3</td>
<td>Abnormal cytokine signaling</td>
</tr>
<tr>
<td>Wiskott Aldrich Syndrome</td>
<td>WASP</td>
<td>Cytoskeletal dysfunction. Treg failure</td>
</tr>
<tr>
<td>ADA-SCID</td>
<td>ADA</td>
<td>?TCR repertoire</td>
</tr>
<tr>
<td>Dock8 deficiency</td>
<td>DOCK8</td>
<td>Unknown</td>
</tr>
<tr>
<td>Omenn Syndrome</td>
<td>Various</td>
<td>Oligoclonal T-cell repertoire</td>
</tr>
<tr>
<td>SAM Syndrome</td>
<td>DSG1</td>
<td>Cell-cell adhesion</td>
</tr>
<tr>
<td>Netherton’s Syndrome</td>
<td>SPINK5</td>
<td>Skin barrier</td>
</tr>
<tr>
<td>Loewys-Dietz Syndrome</td>
<td>TGFBR</td>
<td>?Treg failure</td>
</tr>
<tr>
<td>PLAID</td>
<td>PLCG2</td>
<td>Mast cell signaling</td>
</tr>
</tbody>
</table>
PLAID

- \textbf{PLCG2}-associated
- \textbf{Antibody} deficiency
- \textbf{Immune Dysregulation}

- Evaporative \textbf{cold urticaria} from birth
- Variable immune deficiency, autoimmunity, \textbf{granulomatous disease}
- Gain of function mutation in PLCG2

\textit{Ombrello et al. NEJM 2012}
A novel monogenic allergic disease

Clinical Features
- Severe atopic dermatitis, elevated IgE, food allergy, asthma
- Recurrent bacterial sinopulmonary infection, EBV viremia
- Diffuse demyelination
- Myoclonus, delayed evoked potential
- Neurocognitive delay
- Scoliosis, other bony/CT abnormalities

Laboratory Features
- High IgG, IgA, IgE
- Low class-switched memory B-cells
- Lymphopenia
- Autoantibodies

Zhang et al; Sassi et al, JACI 2014
Phosphoglucomutase 3 – an essential enzyme for glycosylation

Hexosamine Pathway

Glucose

GlcNAc

GlcNAc-6p

PGM3

GlcNAc-1p

UDP-GlcNAc

Cytosol

Golgi/ER

N- and O- linked glycosylation

Naive CD4+ T Cells

Atopic Dermatitis

Control

PGM3 Deficiency

*
Familial hypertryptasemia

- **Cutaneous**
  - Recurrent flushing, itching, angioedema
- **Connective Tissue**
  - Hypermobile joints, retained dentition, scoliosis
- **Atopy**
  - Anaphylaxis, eczema, asthma, food/drug allergy, rhinitis/conjunctivitis
- **Gastrointestinal**
  - Episodic pain, urgency, IBS, reflux, Neuropsychiatric, eosinophilic esophagitis, colitis
- **Neuropsychiatric**
  - tachycardia/dysautonomia, Anxiety/Depression, pain, fatigue, “brain fog”
- Normal bone marrow biopsy

Hypertryptasemia: A dominantly inherited trait

Prevalence of elevated tryptase in the general population


n = 420

Mean: 5.6 µg/L
Geometric mean: 5.8 µg/L
Median: 5.1 µg/L
Range: <1-30.7 µg/L
2.5th percentile: 1.4 µg/L
97.5th percentile: 14.4 µg/L

4.3% (n = 18): >11.4 µg/L
IDENTIFICATION OF A T CELL-DERIVED B CELL GROWTH FACTOR DISTINCT FROM INTERLEUKIN 2

BY MAUREEN HOWARD,* JOHN FARRAR, MARY HILFIKER, BARBARA JOHNSON, KIYOSHI TAKATSU, TOSHIYUKI HAMAOKA, AND WILLIAM E. PAUL

From the Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, and Laboratory of Microbiology and Immunology, National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland 20205; and the Institute for Cancer Research, Osaka University Medical School, Osaka 553 Japan

The importance of murine monokines and lymphokines in T cell immune responses has been emphasized by the development of T cell cloning technology (1) and the identification of cloned tumor lines that respond to or secrete these factors (2, 3). Such studies have shown that the monokine interleukin 1 (IL-1) induces certain T cells to secrete interleukin 2 (IL-2), and that this lymphokine can maintain continuous in vitro proliferation of some T cell subsets. In contrast, the interaction of monokines and lymphokines with B cells is poorly understood, partly because of the lack of assays for B cell function in which contaminating accessory cells capable of mediating secondary effects have been excluded. We have recently described a procedure for the long-term culture of normal mouse B lymphocytes in which induced supernatants from a T cell hybridoma sustain slow proliferation of lipopolysaccharide-activated B cells for periods of up to 12 mo (4). This procedure implied the existence of a T cell-derived growth factor that interacts with activated B lymphocytes to maintain proliferation. Here we identify such a factor in induced supernatants from the mouse thymoma EL4. This material is distinct from previously recognized factors, including IL-2.
From Bench to Bedside: Anti-IL-4R2 therapy
THANK YOU!
Questions?