Update on Immunology

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Disclosures

- Employer
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  - Under $5,000
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  - ACAAI
    - Deputy Editor of Annals of Allergy, Asthma, and Immunology
    - Member, Lit. Review, Annual Mtg., Abst. Rev., and Symposia

Outline

- Allergy background
- Novel T cell subsets
  - Th17
  - Nuocytes
- New and upcoming mechanisms
  - IgE and viral exacerbations of asthma
  - Alternatively activated macrophages
  - Biome

Pathophysiology of Allergic Disease

- Production of specific IgE
- Allergen cross-linking IgE
- Presentation of antigen
- APC

mast cell

- Histamine
- Tryptase
- Eosinophil
- Leukotrienes
- PGD2
- IL-4 & other cytokines

- Damage to epithelium; cellular recruitment

- Eosinophil
- Cells recruited
- Basophil

Can substitute basophile for mast cell; however, no tryptase or PGD2 release.

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CD4 T cell instruction

Th17
- CD4+ T cells
- Associated with the immune response to extracellular pathogens
- IL-17 is a family of 5 members (A-E)
  - Is a chemotactic agent for neutrophils
  - May drive some mucous cell metaplasia
- Have been found in human asthma


Th17 cells – can be Th2, too!

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Nuocytes:
Innate Lymphoid Cells type 2 (ILC2)
- Typical lymphocyte morphology
- Lack cell surface markers of major hematopoietic lineages, but do express
  - CD25 (IL2Ra)
  - CD90 (Thy1)
  - CD117 (c-Kit)
  - CD127 (IL7Ra)
  - CD278 (ICOS)
  - ST2 (IL33R) – so IL-33 responsive
  - IL-17BR – so are IL-25 responsive
- Apparent major source of IL-13
- Also can make IL-5, 6, and 9


Nuocytes
Represent a novel immune cell (innate) that has the ability to modulate nearly all components of the atopic immune response.

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Viruses and atopy: Respiratory syncytial virus

- 80-90% of children have had RSV at least once within the first 2 years of life
- 0.5-2% of infants require hospitalization
  - Especially between 2-6 months of age


Viruses and asthma: Respiratory syncytial virus

Adapted from: Sigurs N. Ped Resp Rev. 2002;3:177-83

Timing is everything.....

Lessons from a mouse model

Evidence of IgE against hRV

- hRV39 is a lab strain of hRV that is not present in the wild
- Serum from 8 subjects obtained
  - 5 subjects had history of working with hRV39
  - 3 subjects had no known history of working with the virus
- hRV39 ELISA used to determine presence of anti-hRV39 IgE

Treatment with anti-IgE inhibited seasonal viral asthma exacerbations

- 419 inner city children with persistent allergic asthma for >1 yr
- Had to be symptomatic or uncontrolled in 6-12 mos prior to entry
- 4 wk run-in and then randomized to omalizumab (208) or placebo (211)
- In a substudy (n=100), 50% (pbo) – 58% (oma) of exacerbations had a respiratory virus identified (usually hRV)
- Virus detection greater with exacerbations (p<0.001)
- No difference in rate of virus detection between the two groups

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Function of macrophage subsets


M2 macrophages as protective of lung disease


M2 macrophages associated with asthma variability

- Bronchoscopy biopsies examined for presence of CD68+ M2 macrophages
  - Mannose receptor or Stabilin-1
- 16 subjects with asthma
  - FEV1 94% (65-114) median (range)
- 9 subjects without asthma
  - FEV1 110% (85-121)
- Biopsy results correlated with PEF variability
Alternatively activated macrophages

- Are found at sites of injury
- Are part of the wound healing response
- However, when these cells become chronically activated they have the ability to drive atopic disease
  - Chronic injury
  - Recurrent acute injury
  - Seasonal allergen exposure, etc.

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The microbiome: what is it, and why do we care?

- We are "supra-organisms" that must co-exist with this complex ecosystem
- 10^{12} viable bacteria/g large bowel content
- 10 times more bacteria in the gut than the body’s own eukaryotic cells
- Genetic content of the biome is 10-100 fold greater than the human genome
- Composition of the biome has significant impact on physiology, immunology, metabolism

The gastrointestinal tract

- Is a critical interface between the individual and the external environment
- The GI mucosal immune system must
  - Prevent and respond to infection
  - Contain colonizing bacteria in the lumen
  - Act as a barrier to bacteria, their products, and antigens
  - Maintain the systemic immune system in a low reactive state
  - Allow for nutrient and water absorption

Mechanisms leading to intestinal dysbiosis and disease

- Host genetics
- Lifestyle
- Early colonization
- Medical practices

Dysbiosis

- Health
  - \( T_{H1}, T_{H2}, T_{H3} \) and others

- Disease
  - \( T_{H1}, T_{H2} \), and others

Nature Reviews | Immunology

Summary/Conclusion I

• The standard Th2 paradigm is no longer valid in light of the multiple mechanistic pathways that can drive atopic disease
• New therapies will be directed at these multiple pathways, and providers need to be aware of their differences

Summary/Conclusion II

• Viruses have the ability to exacerbate atopic disease (and maybe cause)
  • This effect appears to be driven through an IgE mediated pathway
• The microbial communities that coexist in/on us have the ability to modulate our immune responses (amongst others)
  • Future therapies may alter these biomes to promote health and to treat disease