Immunology of Allergy

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Disclosures

None
Why Immunology?

• ABOTO/ AAOA
• New tests
• New treatments
• New variants of disease
• Patients!!!
Objectives

• To review components of the immune system

• To describe the basic immune response

• To highlight immunologic features of allergic responses
What is Immunity?

**Immunity**

From Wikipedia, the free encyclopedia

**Immunity:**

**Medicine**

- Immunity (medical), resistance of an organism to infection or disease.
- Immunity (journal), a scientific journal published by Cell Press

**Law**

- Amnesty law, immunity from past crimes
- Charitable immunity, immunity from liability granted to charities in many countries from the 19th century to the mid-20th century
- Diplomatic immunity, agreement between sovereign governments to exclude diplomats from local laws
- Immunity from prosecution, immunity granted to a witness in exchange for testimony
- Immunity from prosecution (international law), exclusion of governments or their officials from prosecution under international law
- Judicial immunity, immunity of a judge or magistrate in the course of their official duties
- Parliamentary immunity, immunity granted to elected officials during their tenure and in the course of their duties
- Qualified immunity, in the United States, immunity of individuals performing tasks as part of the government's actions
- Sovereign immunity, the prevention of lawsuits or prosecution against rulers or governments without their given consent

**Other**

- Immunity (album), an album by Rupert Hine
- Immunity (reality television), a condition which protects a contestant on a reality TV show from being kicked off the show in a given period
Basic Immune Function
Immune Function: CDC serious diseases

- Viruses: 208
- Bacteria: 538
- Fungi: 317
- Worms: 287
- Protozoa: 57
Immune Functions

• Protection
• Promote normal function
  – Repair wounds
  – Clean-up
  – Remove abnormal cells- cancer
Immune Function

“Self vs Non-self”

• self vs non-self (pathogens)
• non-harmful self vs harmful self (cancer)
• non-harmful non-self (pollen) vs harmful non-self (bacteria)
• Non-harmful non-self (normal flora) vs harmful non-self (abnormal flora)

“Harmful vs Non-harmful”
AUTOIMMUNE DISEASE

ALLERGIC DISEASE

Tolerance

Normal self

Environment
  • dander
  • pollens
  • foods
  • normal flora

NON-SELF

SELF

Immune System

HARMFUL

Neoplasia → Response

Pathogens
  • Bacteria
  • Viruses
  • Fungi
  • Parasites
Antigens

- What is an antigen?
- What is an epitope?
Immune Characteristics

- Surveillance: scan internal environment
- Recognition: self vs non-self
- Specificity
- Clonal expansion: lymphocytes
- Amplification
- Memory
Types of Immunity

• Active verses Passive
• Naturally Acquired vs Artificially Acquired
• Innate vs Adaptive
Active or Passive Immunity

- **Active:**
  - Vaccines induce Ab production in the host
  - Prior infection
- **Passive immunity:**
  - Antidote Ab for snake bite
  - Perinatal Ab
# Protection from Disease

## Barriers
- **skin & mucous membranes** rapidly regenerate, peristaltic movement, mucociliary clearance, vomiting, flow of urine/tears, coughing

## Innate immunity (non-specific)
- **Cellular and humoral defences**
  - dendritic cells, neutrophils, macrophages, NK cells directly identify pathogens
  - lysosome, mucous, stomach acid, complement

## Adaptive immunity (specific)
- **Cellular and humoral defences**
  - antibodies, cytokines, T helper cells, cytotoxic T cells
Adaptive Immunity

- Lymphocytes
- Each cell has 1 receptor and can recognize 1 type of cell
- DNA spicing accounts for antibody variation with endless combinations
- Clonal expansion when activated
- Some fight infections
- Others have memory
Types of Immunity

Immunity

Adaptive Immunity

Innate Immunity

Natural

Passive (maternal)
Active (Infection)

Artificial

Passive (antibody transfer)
Active (immunization)
Immune Components

Cellular elements
- Neutrophils
- Eosinophils
- Basophils
- Macrophages
- Lymphocytes

Soluble elements
- Specific = Ig’s
- Non-specific
  - Cytokines
  - Complement
  - Prostaglandins
  - Leukotrienes
  - Histamine
Immune Cells

- Director cells – orchestrate cellular & cytokine components of inflammation
  Lymphocytes (Th-cells, B-cells, cytotoxic T-lymphocytes), Antigen Presenting Cells

- Effector cells – release of mediators & phagocytosis
  Natural Killer Cells (lymphocytes), Neutrophils, Eosinophils, Mast Cells, Basophils, Macrophages
Cellular Ontogeny

(Adapted with permission from Rolli et al., 1996.)

Antigen Presenting Cells

- Subset of Mononuclear Macrophages Langerhans cells (skin, gut) & Dendritic cells
- Process “foreign” material, present epitope on MHC to T-cells
- Skin, Lymph nodes, Spleen

Major Histocompatibility Complex

Class I: ALL CELLS
- Regulation of immune responses to endogenous epitopes, with “self vs. non-self” identification for Cytotoxic T-cells and Natural Killer Cells
- Present on all nucleated cells

Class II: APC’s
- Regulation of immune responses to exogenous pathogens, presented by APCs to Helper T-cells and B-cells
- Restricted to dendritic, B-cells, macrophages
Neutrophil
The First Responder:

- Initial cell to respond to infection
- Make nasty chemicals that kill microbes and damage tissue
- Short-lived
- Monocytes come in next and either fight or clean up depending on cytokines present
Mast Cells/Basophils

- **Basophils**
  - contain histamine
  - in circulation

- **Mast Cells**
  - \( \frac{1}{2} \) cell volume is secretory granules
  - Submucosal/ perivascular locations

- **Have director and effector roles**
  - Mast cells (IL-3, IL-4, IL-5, IL-9, tryptase, leukotriene, prostaglandin)
  - Basophils (IL-4, IL-13)
Eosinophils

- 1-5% of circulating granulocytes
- Most abundant in tissues with mucosal interface (GI, Resp, GU)
- Secretary granules - Helminthotoxic
  - Major basic protein (Cytotoxic)
  - Eosinophilic cationic protein (Neurotoxic)
- Roles in Host defense/damage
  - Chiefly effective against large non-phagocytosable organisms
  - Can be bacteriocidal
  - Mediators of Inflammation
  - Hyperactivity of airway, ciliary dysfunction, epithelial disruption

Lymphocytes

Natural Killer Cells

- Have no Ab or T cell receptors
- 5-20% of lymphocytes (from bone marrow)
- Non-specific (innate) and adaptive response
- Target virally infected or malignant cells
- Induce apoptosis through toxic granules & ligands

T Lymphocytes

- arise in bone marrow, mature in thymus
- 65% of circulating lymphocytes
- cell-mediated defense: T-Helper, cytotoxic, T-regulatory

T Lymphocytes

- CD4 T-cells (T-helper) Th-1 & Th-2 recognize antigen presented by MHC II molecules (APCs, B-cells, macrophages)
- CD8 T-cells (cytotoxic), recognize antigen presented by MHC I molecules, target viruses, tumors, transplanted organs
TH1 verses TH2

\[ T_{H1} \]
- IFN-γ
- TNF-β

\[ T_{H2} \]
- IL-4, IL-5
- IL-9, IL-13

**Immune defence against:**
- Intracellular pathogens

**Unfavorable responses to:**
- Autoantigens (diabetes, inflammatory bowel disease)

**Immune defence against:**
- Ectoparasites
- Gastrointestinal worms

**Unfavorable responses to:**
- Allergens (asthma, allergy)

(Modified from Herrick CA, Bottomly K: To respond or not to respond: T-cells in allergic asthma. Nature Rev Immunol 2003;3:405-412.)
T-reg Cells

Moingeon P et al. Allergy 2006;61:151-165
B cells

- Antigen-specific surface receptors
- Original naïve population encompasses ~ $10^6$ different variable region receptors
- Activate via:
  - APC presentation of specific antigen
  - Th2 interaction (cell to cell plus cytokine effects)
- Produce antigen specific IgG, IgA, IgE, IgM
B cells

• Naïve B-cells express non-specific IgM, IgD
• After activation, isotype (class) switch to produce antigen specific IgG, IgA, IgE or (specific) IgM
• Differentiate into antigen specific:
  • Plasma cell (short-lived immunoglobulin producing “factory”)
  • Memory cell (long lived, augment body’s reaction to later contact with same antigen)
Surface Receptors

Surface Immunoglobulin
- Antigen-binding site
- Light chain
- Heavy chain
- Transmembrane region

Antibody
- Variable regions
- Constant regions
- Transmembrane region

T-cell receptor
- Antigen-binding site
- α chain
- β chain

The American Academy of Otolaryngic Allergy
Immunoglobulins

- IgG – preponderant blood bourne antibody, response to pathogens; only antibody that crosses placenta
- IgA – primary secreted antibody in milk, mucous, tears, saliva, etc.; combats colonization
- IgM – first response to pathogens, can be secreted through mucous membranes (with J-chain)
- IgE – binds to allergens and parasites; cross-linking on mast cells, basophils and eosinophils causes degranulation
- IgD – antigen receptor on naïve B-cells
Immunoglobulin Function

- Neutralization
- Agglutination
- Opsonization
- Antibody Dependent Cytotoxicity
- Bind to Mediator Cells & Cause Degranulation – IgE
- Activation of Complement
Immunoglobulin distribution

IgG = 75%

- IgG₁ = 66%
- IgG₂ = 20%
- IgG₃ = 10%
- IgG₄ = 4%
- IgA = 15%
- IgM = 10%
- IgE = <1%
- IgD = <0.1%
Adaptive Immunity - memory

- Antibody titre
  - 1° response to antigen A
  - Seeding to memory
  - 2° response to antigen A
  - 1° response to antigen B

- Lymphocyte proliferation to Ag A
- Lymphocyte proliferation to Ag B

Days:
- http://www.le.ac.uk/microbiology/website/lecturespage.htm
Cytokines

- LMW proteins that bind to specific receptors & induce/enhance/inhibit genes & behaviors

- 4 Basic Families:
  - Type 1 or hematopoietic
    - IL-4, Th-2 differentiation & IgE production inducer
    - IL-5, production & survival of eosinophils
    - IL-13, similar spectrum of effects as with IL-4/5,
    - IL-12, induce Th-1 differentiation response to infection
  - Type II
    - IFN-γ, proinflammatory
    - IL-10, down-regulates inflammatory cytokines
  - Tumor Necrosis Factors
  - Chemokines (cellular attractants)
Chemical Mediators

Allergic Rhinitis

• Cytokines:
  – IL4, IL5, IL13

• Eicosanoids:
  – Prostaglandins: PGE2
  – Leukotrienes: LTB4 and LTC4

• Histamine
Histamine

• Primary mediator from Mast Cells/Basophils of early or “immediate” phase
• Signs commence at ~ 5 min & peak ~ 30 min
• Incites vasodilatation; increase in vascular permeability, heart rate & force of contraction
• Goblet & bronchial gland secretion, smooth muscle contraction in bronchial tree
• Pruritis

http://en.wikipedia.org/wiki/Histamine

Complement

- Enzymatic proteins
- Direct attack or opsonization
- Chemoattractant molecule
- Classical: Antibody dependent
- Alternative: Direct activation (innate)
Response to Infection: Inflammation

- Dendritic cells recognize characteristic features of infectious agent (innate immunity)
- Secrete cytokines - act on neighboring cells
- Blood vessels put adhesion molecules on their surface to recruit immune cells, and become leaky to allow for antibodies to diffuse to tissue
- Inflammation is good for infection
Defense against worms and biting insects

- T helper promote Ige to stimulate basophils and mast cells to strengthen barriers at the skin, gut, and lung
- Attract eosinophils to the site of infection
  - good at attacking worms
  - sneezing, itching, coughing, diarrhea
Allergy: (von Pirquet 1906) altered reactivity to a foreign substance after prior experience, whether helpful or harmful to host.
Gel and Coombs

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE-Mediated Hypersensitivity</td>
<td>Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators. Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema.</td>
</tr>
<tr>
<td>II</td>
<td>IgG-Mediated Cytotoxic Hypersensitivity</td>
<td>Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC. Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia.</td>
</tr>
<tr>
<td>III</td>
<td>Immune Complex-Mediated Hypersensitivity</td>
<td>Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils. Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.</td>
</tr>
<tr>
<td>IV</td>
<td>Cell-Mediated Hypersensitivity</td>
<td>Sensitized Th1 cells release cytokines that activate macrophages or Tc cells which mediate direct cellular damage. Typical manifestations include contact dermatitis, tubercular lesions and graft rejection.</td>
</tr>
</tbody>
</table>
Pathophysiology of allergic rhinitis

- An allergen enters a susceptible organism
- Allergen is presented by antigen presenting cells to T Cells resulting in Th2 differentiation of the T Cell
- Th2 T Cells then begin producing IL-4 and IL-13 which trigger IgE synthesis
- IgE cells bind high affinity receptor on mast cells
- Degranulation of mast cells releases histamine + LT
- Th2 cells also synthesize IL-5 attract eosinophils
- Eosinophils release major basic protein
Hygiene Hypothesis

- D Strachan: Family size, infection and atopy: the first decade of the "hygiene hypothesis". Thorax 2000;55:suppl 1:S2-10

- Based upon the epidemiology of hay fever - “Declining family size, improved household amenities, and higher standards of personal cleanliness have reduced the opportunities for cross-infection in young families. This may have resulted in more widespread clinical expression of atopic disease"

- ..can be interpreted in terms of failure to modulate default Th2 responses

http://en.wikipedia.org/wiki/Allergy
http://www.le.ac.uk/microbiology/website/lecturespage.htm
"Normal" Progression of Immune Bias in Early Childhood

The intrauterine environment is powerfully Th2 – this imprints Th2 dominance upon the neonate.

Serial infections

Age

Balanced Th1/Th2 at ~2yr

Immune response

Th2

Th1

http://en.wikipedia.org/wiki/Allergy
http://www.le.ac.uk/microbiology/website/lecturespage.htm
Progression of Immune Bias per Hygiene Hypothesis

Fewer serial infections – hygiene, small family size, less facility daycare....

Immune response

Longer period of time in which to make and establish Th2 responses to environmental antigens (i.e. allergens)

Unbalanced Th1/Th2 Th2 dominance at ~2yr

http://en.wikipedia.org/wiki/Allergy
http://www.le.ac.uk/microbiology/website/lecturespage.htm
Immune System Balance

Up-regulation

Infection, Autoimmunity

Th1
IFN-γ, IL-2
TNF-β

Th2
IL-4, IL-5
IL-13

Immunotherapy

TGF-β
IL-10

T-Reg

Down-regulation

“Allergy”

Up-regulation

TNF-α
IL-12
Allergen-induced release of histamine by mast cells in skin is primary cause of rapid onset of localized swelling.
Mediators in Mast Cells / Basophils

Antigen

Allergen-IgE activated mast cell or basophil

Preformed mediators

Generated mediators

Cellular attractants
- NCF → Neutrophils
- ECF-A → Eosinophils, monocytes
- LTB₄ → Lymphocytes

Inflammatory agents
- Histamine → Vasodilation, vascular permeability
- PAF → Microthrombus formation, tissue damage
- Tryptase* → Proteolysis, C₃a activation
- Kinins → Vasodilation, edema

Spasmogens, mucus secretion
- Histamine → Bronchial smooth muscle contraction
- PGD₂* → Mucus secretion
- LTC₄ → Mucus secretion
- LTD₄ → Mucosal edema

*Tryptase and PGD₂ produced mostly by mast cells

(Adapted with permission from Roitt et al., 1995.)

Mediators in Eosinophils

IgE-crosslinking by allergen

Preformed mediators (minutes)
- Histamine
- Proteases
- Proteoglycans
- TNF-α

Newly formed eicosanoids (minutes)
- Cysteinyl leukotrienes
- PGD₂, LTB₄

Induced cytokines/chemokines (hours)
- IL-3
- IL-4
- IL-5
- IL-6
- IL-8
- IL-9
- IL-11
- IL-13

MIP-1α
- MIP-1β
- MCP-1
- TNF-α

Early (Edema, bronchoconstriction, vaso-permeability)

Late (Inflammation, cell recruitment)

Acute Phase (Immediate) & Late Phase (Delayed) Responses