Hypersensitivity

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Timeline

1893 - Emil von Behring
- Working with diphtheria toxin noted that animals would suffer enhanced responses and even death following a second dose of toxin too small to injure normal untreated animals
- Described this phenomenon as “hypersensitivity”

1902 - Charles Richet and Paul Portier
- Set sail on the yacht of the Prince of Monaco to study the effects of marine toxins in mammals
- Attempted to protect dogs from the effects of toxins by inoculating them at low doses
- Re-exposure to innocuous doses resulted in a rapid shock and suffocation
- Coined the term “ana-phylaxis” to emphasize its antithesis to the familiar “prophylaxis”

1903 - Maurice Arthus
- Described a stereotypical response in rabbits following repeated intradermal injection of protein antigens
- The response, characterized by local erythema, induration, hemorrhage and necrosis became known as the “Arthus Reaction”

1906 - Clemens von Pirquet and Bela Schick
- Coined the term “serum sickness” to describe strange systemic symptoms suffered by some patients weeks after receiving diphtheria or tetanus anti-toxin horse serum
- Postulated for the first time that these hypersensitivity reactions might be the product of immune response
- Named these responses “allergic” from the Greek allos ergos, altered reactivity.

Definitions

Hypersensitivity:
- Broadest (Abbas) - Disorders caused by immune responses
- Dysregulated response to foreign antigen
- Failure of tolerance to self-antigen
- Practical - Used clinically to refer to aberrant or excessive immune responses generated against foreign antigens, although the same immune processes apply in many autoimmune disease

Allergy:
- Symptoms elicited by encounter with foreign antigen in a previously sensitized individual
Manifestations of Hypersensitivity

<table>
<thead>
<tr>
<th>Site of Exposure</th>
<th>Syndrome</th>
<th>Common Allergens</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Mucosa</td>
<td>Allergic Rhinitis</td>
<td></td>
<td>Nasal Polyps</td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
<td></td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>G.I. Mucosa</td>
<td>Food Allergy</td>
<td></td>
<td>Cramping, Vomiting, Anaphylaxis</td>
</tr>
</tbody>
</table>

Symptoms frequently are localized to the anatomical site of antigen exposure:

Common to All Types

- Products of the adaptive immune system
  - Require at least one exposure for sensitization to occur
  - Sensitization can be long lived in the absence of re-exposure (>10 years) due to immunologic memory

Type I (Immediate) Hypersensitivity

- Antigens:
  - Classically exogenous, as opposed to “self” (autoimmune)
  - Contact via mucous membranes and at low dose appears to favor type I sensitization
- Reactions:
  - Occur within seconds-minutes of exposure
  - Severity ranges from irritating to fatal
- Immune Effect
  - Initial antigen contact leads to IgE production
  - On re-exposure, antigen-specific IgE initiates the reaction

IgE Production

- Occurs as part of a secondary immune response (generally multiple or persistent exposures)
- Class switch to IgE is directed by IL-4 and IL-13 (Th2 cytokines), and requires T cell help (CD40L)
- The propensity to make an IgE response to environmental antigens varies among individuals
- “Atopic” individuals are those genetically predisposed to form IgE responses. That is, atopy is heritable
Genetics of Atopy

- Complex, multigenic heritability. Candidate genes:
  - Chrom. 11q - β-subunit of the high affinity FcεRI
  - Chrom. 5q - Cytokine cluster: IL-3, IL-4, IL-5, IL-9, IL-13
  - TIM (T-cell, Ig domain, Mucin domain) - surface protein, variation associated with IL-4/IL-13 production
  - IL-12 p40 subunit (associated with asthma and AD)

- Variation in IgE response to specific allergens is associated with MHC II genetics
  - *DRB1*1501 is associated with IgE responses to specific ragweed pollen proteins

Allergy Epidemic

- Type I Hypersensitivity diseases, including asthma and allergic rhinitis, have been increasing in prevalence in the economically "advantaged" parts of the world for 30 years
  - The "hygiene hypothesis" attributes increased allergic disease rates to generally decreasing microbial exposure in early life which would normally provide a Th1-promoting effect
    - Neonatal bias: ↓IL-12 (DC) and ↓IFN-γ (T cells)
    - Birth order: ↑allergy rates among 3rd- and 4th-born children
    - Protective effect of day care
    - 1990 - East/West Berlin immediately after the wall fell: East had ↓vaccination rates, ↑prev. childhood infection, but ↓ed asthma
    - Hx of measles or HAV infection, or +PPD ↓allergy rates

Allergy: Sensitization Phase

- Serum IgE produced by plasma cells has a short T½ (serum T½IgG = 30 days; for IgE = 2 days)
- Rapidly taken up by FcεRI on tissue mast cells and circulating basophils

Allergy: Effector Phase

- Early Phase Response: within seconds-minutes
  - IgE crosslinking by antigen → release of preformed mediators
    - histamine → smooth muscle constriction, mucous secretion, ↑vascular permeability, ↑GI motility, sensory nerve stimulation

Allergy Epidemic

- Weighing against the Hygiene Hypothesis:
  - Despite this epidemiologic data, some evidence is hard to reconcile
    - Previous infection with helminths, which generates a strong Th2 response, is also associated with protection against allergy
    - Early life exposure to pathogens is also associated with a decreased risk of autoimmune disease (e.g., type 1 diabetes), a classic Th1-mediated condition
    - Revised hygiene hypothesis - early life exposure to microbial pathogens influences the balance of immune responsive vs. immune modulating influences
Allergy: Effector Phase

• **Early Phase Response:** within seconds-minutes
  - IgE crosslinking by antigen ➔ release of preformed mediators
  - Histamine ➔ smooth muscle constriction, mucous secretion, ↑vascular permeability, ↑GI motility, sens. nerve stimulation

• **Late Phase Response:** 6-24 hours after exposure
  - Mast cell production of newly synthesized mediators
  - Leukotrienes ➔ smooth mm. contraction, vasodil., chemotaxis
  - Cytokines ➔ recruitment of PMN and eosinophils

FcεRI Signaling

• **Structure:**
  - Alpha, Beta, Gamma-Gamma
  - Alpha - binds IgE monomer
  - Beta, Gamma - signal
  - ITAM’s
  - Conserved sequences within the receptor tail containing tyrosines
  - ITAM Tyr is phosphorylated on ligand binding
  - Serve as docking sites for downstream activating kinases

Eosinophils

• Innate responder cell in Type I hypersensitivity
  - Production in marrow induced by IL-3, IL-5, GM-CSF
  - Chemotaxis to tissue sites: IL-5, Eotaxin-1, 2, 3
  - "Primed" by IL-5, eotaxins, C5a
  - ↑FcγR and C' receptor expression
  - ▼threshold for degranulation
  - On activation, eosinophils secrete
    - Toxic proteins: major basic protein, eos. cationic protein, eos. derived neurotoxin
    - IL-3, IL-5, GM-CSF, IL-8
    - LT’s

Mast Cell Degranulation

Pre-exposure to Ag - Post-exposure to Ag

Evolutionary Role of Type I Response

• Mast cells line all subepithelial mucosa
  - Rapid recruitment of PMN, eosinophils, monocytes to sites of pathogen entry
  - ▲Lymph flow from peripheral sites to lymph node
  - ▲GI motility favors expulsion of GI pathogens
• Important role in parasite clearance
  - c-kit⁻/⁻ mice have no mast cells ▲susceptibility to trichinella, strongyloids
  - Eosinophil depletion (Ab-mediated) ▲severity of schistosomal infection
Evolutionary Role of Type I Response

- STAT6:
  - Mediates IL-4/IL-13 signaling
  - Required for IgE class switch
  - STAT6−/− mice have no IgE
- Wild type or STAT6−/− mice were injected with 500 N. brasiliensis larvae
- Worm counts and fecal egg counts were assessed at 13 days

Anaphylaxis

- Response to systemic circulation of allergen
  - Triggering of mast cells in peri-vascular tissue
  - Circulating histamine, PG's/LT's, vascular leak, vasodilatation
  - High-output shock (increased cardiac output, ↓↓ BP)
- Other symptoms: urticaria, flushing, wheeze, laryngeal edema with airway compromise, G.I. cramping, diarrhea
- Rapid progression over seconds-minutes
- Treatment:
  - Early administration epinephrine I.M., followed by antihistamines (H1 and H2 blockade) √ treat early phase
  - Subsequent administration corticosteroids √ prevent late phase

Type I Sensitivity in Allergy

- Type I Hypersensitivity mediates:
  - Allergic Rhinitis/conjunctivitis (Hayfever)
  - Asthma
  - Food/Medication reactions
  - Contact urticaria
  - Some forms of eczema
  - Anaphylaxis - food, bee sting, drug, exercise-induced

Type II Hypersensitivity: Antibody (Ab) Mediated

- Target-specific IgM and IgG mediate damage
- Targets:
  - Self-molecules altered by foreign antigen √ neo-epitope
  - Penicillin conjugates to RBC surface proteins √ new penicilloated-protein serves as a target for IgM/IgG √ intravascular hemolysis
  - Self-molecules unaltered = breaking of tolerance
    - Group A Strep pharyngitis yields Ab's to the Strep M protein √ Ab's cross react with cardiac muscle and valves √ scarring

Type I Sensitivity in Allergy

- Documenting allergic sensitivity: skin testing
  - Allergenic extract (airborne, food, venom) is introduced by prick or injection intracutaneously
  - Sensitization is evident within 15-20 minutes as a wheal/flare at the allergen introduction site

Type II Hypersensitivity: Ab Functions

- The mechanisms of type II hypersensitivity are exactly the those of normal Ab function, plus some:

<table>
<thead>
<tr>
<th>Ab Function</th>
<th>Target</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opsonization</td>
<td>Phagocyte surface</td>
<td>Splenic clearance, bronchoconstriction</td>
</tr>
<tr>
<td>Neutralization</td>
<td>Acetylcholine receptor</td>
<td>Myasthenia Gravis</td>
</tr>
<tr>
<td>ADCC</td>
<td>Glomerular basement membrane proteins</td>
<td>Goodpasture's Disease</td>
</tr>
<tr>
<td>C Fixation</td>
<td>Penicilloyl-RBC protein conjugates</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Non-Physiologic</td>
<td>TSH receptor</td>
<td>Grave's Disease</td>
</tr>
</tbody>
</table>
Type III Hypersensitivity: Immune Complex Mediated

- First Description: Arthus Reaction
  - Rabbit received horse serum containing anti-toxin antibody
  - After several days, antigen (toxin) was injected subcutaneously
  - Classic Arthus reaction occurs within 5-8 hours:
    - Local erythema/tenderness with edema, necrosis, hemorrhage

- Arthus Reaction
  - Immune Mechanism
    - Antibody-Antigen complexes form within blood vessel walls
    - Complement fixation generates C5a
      - Neutrophil chemoattractant
      - PMN infiltration
      - Anaphylatoxin - local mast cell histamine release
      - Neutrophil activation by FcγR's
      - Release of cytotoxic enzymes
      - Platelet aggregation by FcγR's
      - Small vessel thrombosis, necrosis
      - Local macrophage release of IL-1, TNF-α, and IL-8 - propagation

- Serum Sickness: Systemic Arthus-like reaction
    - Rash, fever, lymphadenopathy and arthralgias in recipients of anti-diphtheria antiserum made in horses (hint: 2-3 weeks post-infusion)

- Rabbit Model (Dixon and Lambert, 1960's):
  - Injection of radiolabeled bovine serum albumin (BSA) day zero
  - Serum BSA and anti-BSA antibody levels were tracked
  - Look for serum immune complexes and proteinuria

Importance of C5a in I.C. Disease

- Mouse Model of Immune Complex Disease:
  - Infuse Anti-ovalbumin Ab via trachea, ovalbumin via I.V.
  - I.C.'s form at respiratory capillaries, examine histology at 4 hours

- Importance of FcγR's in I.C. Disease
  - B/W Mouse - spontaneous accumulation of I.C.'s in the glomerulus
  - FcγRI and FcγRIII - contain ITAM's, activating for phagocytes
  - γ-chain knockout (γ-/-): Lacks expression of FcγRI and FcγRIII
Immunology Wars

• Epic Immunologic Battle: 1870-1950
  - "Humoralists" (France): Hypersensitivity is mediated by serum factors
  - vs.
  - "Cellularists" (Germany): Hypersensitivity is mediated by phagocytes
• By 1915, the Humoralists appeared to have won
  - Hay fever, asthma, anaphylaxis
  - Drug-induced hemolysis 

Delayed Type Hypersensitivity

• Group of related responses to antigen, all dependent on cell-mediated immunity
• Although prior sensitization is required, reactions occur over 1-3 days following re-exposure
• T cells: necessary and sufficient to elicit the reaction
  - Athymic subjects (animal or human) are not sensitizable
  - T cell depletion (via anti-T cell Ab’s) reverses sensitization
  - Transfer of purified T cells confers sensitization

Type IV Hypersensitivity: Tuberculin Reaction

• 1892 - Robert Koch
  - Discoverer of tubercle bacillus
  - Attempted to prevent TB by inoculation with bacillus extract
  - Unfortunately:
    ‐ No protection for naive individ.
    ‐ Reactivated disease in exposed
  - But: intradermal injection of bacillus extract in previously exposed individuals resulted in a stereotypic indurated lesion within 48-72 hours

Type IV Hypersensitivity: Delayed Type

• 1942 - Karl Landsteiner and Merrill Chase
  - Demonstrated transfer of tuberculin test sensitivity in guinea pigs
  - Sensitivity is transferred from TB-exposed to unexposed animals with leukocyte transfer, but not with serum transfer
  - Redemption for the Cellularists

Varieties of DTH Reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Reaction Time</th>
<th>Clinical Appearance</th>
<th>Histology</th>
<th>Site/ Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact</td>
<td>48-72 hours</td>
<td>Eczema</td>
<td>T cells followed by macrophages, edema of the epidermis</td>
<td>Epidermal, organic mols., poison ivy, heavy metals</td>
</tr>
<tr>
<td>Tuberculin</td>
<td>48-72 hours</td>
<td>Local Induration</td>
<td>T cells, monocytes, macrophages, basophils, fibrin deposition/edema</td>
<td>Intradermal: PPD, candida, mumps</td>
</tr>
<tr>
<td>Granuloma</td>
<td>21-28 days</td>
<td>Hardened Nodular</td>
<td>Macrophages, epithelioid giant cells, fibrosis</td>
<td>Skin, viscera: persistent Ag (TB, leprosy)</td>
</tr>
</tbody>
</table>

Common to all DTH Reactions

• Histology of the DTH reaction:
  - T Cells - CD4 (Th1); some forms CD8
  - Macrophages/monocytes
  - Basophils
  - Fibrin
  - If persistent antigen: multinucleated giant cells; granulomata
• Cytokines found at the site of a DTH reaction:
  - IL-2
  - IFN-γ
  - TNF-α
  - Macrophage chemotactic protein (CCL-2)
Contact Sensitivity: Hapten DTH

• Phase One: Initial Exposure - Sensitization
  - Hapten: a small organic molecule, frequently lipophilic, crossing the epidermal barrier by diffusion, associates with cell proteins
    - Chromates (leather tanning), unashol (poison ivy), nickel
  - Haptenated proteins are taken up by Langerhans' cells - peptides bearing hapten are loaded onto MHC I and MHC II
  - LC's migrate to regional lymph nodes, activate naive T cells

• Phase Two: Re-exposure - Elicitation
  - Hapten-specific memory T cells bearing the cutaneous lymphocyte antigen (CLA-1) continuously migrate between lymphatics and skin
  - Re-encounter with haptenylated protein may occur on:
    - Langerhans' cell (MHC II): Th1 cell secretion of IFN-γ, MCP-1 with macrophage recruitment
    - Keratinocyte (MHC I) (lipophilic hapten): CD8 CTL activation, release of perforins and granzyme, local tissue damage

Contact Sensitivity: Hapten DTH

Penicillin Mediates All Types of Hypersensitivity

• Immune-mediated adverse reactions occur at a rate of 1 per 100 administrations

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE-mediated</td>
<td>Acute anaphylaxis, urticaria</td>
</tr>
<tr>
<td>II</td>
<td>C'-mediated cytolysis</td>
<td>Hemolytic anemia, thrombocytopenia</td>
</tr>
<tr>
<td>III</td>
<td>Immune Complex Damage</td>
<td>Serum sickness, drug fever, vasculitis</td>
</tr>
<tr>
<td>IV</td>
<td>T Cell mediated</td>
<td>Contact sensitivity</td>
</tr>
</tbody>
</table>

Hypersensitivity Progression

• Antigen-specific responses may progress from one type of hypersensitivity to another:
  - Latex allergy among healthcare workers
    - Initial reaction is typically a contact sensitivity (type IV reaction)
    - With recurrent latex contact, sensitivity progresses to latex-specific IgE, imparting risk of anaphylaxis
  - p-aminobenzoic acid (PABA), the active ingredient in many sunscreens, can act as a contact sensitizer
    - PABA DTH reactivity is associated with ↑ed risk of immediate type hypersensitivity to local anaesthetics (e.g., benzocaine) due to cross-reactivity of the aromatic core