Hypersensitivity

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Origins of Hypersensitivity

• "Hypersensitivity" first used clinically in 1893:
  - During attempts to protect against diphtheria toxin, it was found that an animal would suffer enhanced responses and even death following its second exposure to toxin at a dose too small to injure normal untreated animals

• The term “Allergy” is coined in 1906:
  - These hypersensitivity reactions were postulated to be the product of an “allergic” immune response, derived 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 diseases

• Allergy:
  - Symptoms elicited by encounter with foreign antigen in a previously sensitized individual

Manifestations of Hypersensitivity

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

<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>Nasal Pruritis, Runny Nose, Congestion</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td>Bronchospasm, Chronic Airway Inflammation</td>
<td></td>
</tr>
<tr>
<td>G.I. Mucosa, Food Allergy</td>
<td></td>
<td>Cramping, Vomit/Diarrhea, Anaphylaxis</td>
<td></td>
</tr>
</tbody>
</table>

Hypersensitivity: Gell & Coombs Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Immediate Hypersensitivity</th>
<th>Bystander Reaction</th>
<th>Immune Complex Disease</th>
<th>Delayed-type Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Peanut Anaphylaxis</td>
<td>PCN-associated Hemolysis</td>
<td>Serum sickness</td>
<td>Contact Dermatitis (in'), PPD</td>
</tr>
<tr>
<td>Example</td>
<td>IgE</td>
<td>IgG Monomer, IgG Multimers</td>
<td>CD4 T cell</td>
<td>CD8 T cell</td>
</tr>
<tr>
<td>Mediator</td>
<td>Soluble</td>
<td>Soluble</td>
<td>Soluble</td>
<td>Cell-associated</td>
</tr>
<tr>
<td>Antigen</td>
<td>Mast Cell Activation</td>
<td>Complement FcγR cells</td>
<td>Complement Pathway, Mφ</td>
<td>Cytotoxicity (perforin/granzyme)</td>
</tr>
</tbody>
</table>
**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
  - Antigen is a protein or is capable of complexing with protein (e.g., nickel ion, penicillin)

**Type I (Immediate) Hypersensitivity**

- **Antigens:**
  - Exogenous, otherwise innocuous
  - Contact typically occurs via mucous membranes (respiratory, GI) and at low dose
- **Immune Mechanism**
  - Antigen contact first leads to IgE production: Sensitization
  - On re-exposure, pre-formed antigen-specific IgE triggers mast cell activation resulting in symptoms: hive, wheeze, itch, cramps
- **Reactions:**
  - Occur within seconds-minutes of exposure
  - Severity ranges from irritating to fatal

**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 via CD40L
- The propensity to make an IgE response to environmental antigens varies among individuals
- “Atopic” individuals are those with an inherited predisposition to form IgE responses

**Type I Rxn: Sensitization Stage**

- IgE produced by plasma cells has a short circulating half-life (serum $T_{1/2}$~2 days; comp. to IgG~30 days)
- Rapidly taken up by FcεRI on tissue mast cells and circulating basophils

**Type I Rxn: Effector Stage**

- **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. constriction, vasodil., mucous prod.
    - Cytokines → recruitment of PMN and eosinophils
Receptors

Structure:
- Alpha- binds IgE monomer
- Gamma- shared by IgG FcR’s I & III

Receptors are aggregated
- When pre-bound IgE binds multivalent Ag
- Initiates ITAM phosphorylation

ITAM’s
- Conserved tyrosine-containing sequence motifs within a variety of receptors (TCR, BCR, FcRs)
- Serve as docking sites for downstream activating kinases, in this case, Syk

Activating kinases, in this case, Syk
Serve as docking sites for downstream motifs within a variety of receptors (TCR, BCR, FcRs)

Immunoreceptor
Tyrosine-based
Activation
Motif

FcεRI Signaling

Mast Cell Degranulation

Pre-exposure to Ag
Post-exposure to Ag

Eosinophils

- Innate responder cell in Type I hypersensitivity
- Production: Induced in the bone marrow by:
  - IL-5 – Th2 cytokine, drives specifically eosinophil production
  - IL-3, GM-CSF – drive granulocyte production in general
- Chemotaxis: Homing to tissue sites utilizes:
  - IL-5, Eotaxins-1, -2, -3
- “Primed” for activation by IL-5, eotaxins, C3a & C5a
  - FcεRI & FcεR expression; Cε receptor expression
  - Induce FcεR expression
  - Threshold for degranulation

Activation:
- Most potent trigger is Ig-crosslinking (IgA>IgG>IgE)
- Potentiated by IL-5, GM-CSF, granule proteins (MBP), C3a/C5a
- Results in exocytosis of pre-formed eosinophil toxic proteins

Anti-microbial effect:
- Major basic protein
- Eosinophil cationic protein
- Eosinophil-derived neurotoxin
  - All have pI’s >10
  - Directly toxic to helminths
  - Also cause tissue damage

Mobilize more innate responders
- Secretion of IL-3, IL-5, GM-CSF (more eos), IL-8 (PMN)
- Elaboration of LT-C4, -D4

Eosinophils

Evolutionary Role of Type I Response

- Mast cells line all subepithelial mucosa
  - Rapid recruitment of PMN, eosinophils, monocytes to sites of pathogen entry
  - 0/Lymph flow from peripheral sites to lymph node
  - G.I. motility favors expulsion of G.I. pathogens

- Important role in parasite clearance
  - c-kit-/- mice have no mast cells
  - Susceptibility to Trichinella, Strongyloides
  - Eosinophil depletion (Ab-mediated) 0 severity of schistosomal infection

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: 0/IL-12 (DC) and 0/IFN-γ (T cells)
  - Birth order: 0 allergy rates among 3rd- and 4th-born children
  - Protective effect of day care
  - Hi of measles or HAV infection, or 0/HPD = 0 allergy rates
  - 1990 - East/West Berlin immediately after the wall fell: East had
  - 0 vaccination rates, 0 prev. childhood infection, but 0 vol asthma

- gamma- shared by IgG FcR
- alpha- binds IgE monomer
**Type II Hypersensitivity**

- **Antibody-mediated “Bystander Reactions”**
  - Immune effector is target-specific IgM and IgG
  - (Contrast with Type III Reactions in which the Ig is not specific for the tissue being damaged)

- **Clinical Manifestations:**
  - Classically manifests as a reaction to a foreign substance (most commonly a drug) acting as a hapten
  - The same mechanisms, however, manifest with autoimmunity through the process of molecular mimickry

**Anaphylaxis**

- **Response to systemic circulation of allergen**
  - Triggering of mast cells in peri-vascular tissue
  - Circulating histamine, PG’s/LTC4...vasodilatation, vascular leak
  - High-output shock: ↓BP despite ↑ed cardiac output
  - Other symptoms: flushing, urticaria, wheeze, laryngeal edema with airway compromise, G.I. cramping, diarrhea

- **Rapid progression over seconds to minutes**

- **Treatment**
  - immediate administration epinephrine I.M., followed by antihistamines (H1 and H2 blockade) → treat early phase
  - subsequent administration corticosteroids → prevent late phase

**Type I Hypersensitivity in Allergy**

- **Manifestations of Type I Hypersensitivity:**
  - Allergic Rhinitis/conjunctivitis (“Hayfever”)
  - Asthma - prevalence >60% in the past 20 years
  - Food/Medication reactions - urticaria (hives)
  - Contact urticaria
  - Some forms of eczema
  - Anaphylaxis - systemic reaction induced by food, venom, medication, etc.

**Demonstrating Type I Hypersensitivity in the Patient**

- **Documenting allergenic sensitivity**: skin testing
  - Allergen (airborne, food, venom, some medications) is introduced by prick or intradermal injection
  - Sensitization is evident within 15-20 minutes as a wheal/flare at the allergen introduction site

**Type II Hypersensitivity**

- **Drug Reactions**
  - Hapten - a molecule too small to elicit an immune response itself, but capable of covalent conjugation to self proteins, creating a new (non-self) target or epitope
  - example: penicillin is metabolized to yield the penicilloyl moiety which binds surface proteins on blood cells and platelets
  - penicilloyl-proteins represent neoepitopes → break tolerance

- **Molecular Mimickry**
  - Pathogen elicits an appropriate Ab response
  - Ab cross-reacts with self-tissue (very similar epitopes)
  - Group A Strep pharyngitis yields Ab’s to the Strep M protein → Ab’s cross react with cardiac muscle and valves → scarring

**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 decreased risk of autoimmune disease (e.g., type I 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, not simply Th1-Th2 balance

**Manifestations:**

- **Type I Hypersensitivity**
  - Immediate (within minutes) reaction
  - Elicits IgE to specific allergens
  - Symptoms: urticaria, laryngeal edema, bronchial asthma

- **Type II Hypersensitivity**
  - Delayed (within hours) reaction
  - Elicits antibodies against self antigens
  - Symptoms: autoimmune diseases, certain drug reactions
Mechanisms of Type II Hypersensitivity: Exactly those of normal Ab function (plus some):

<table>
<thead>
<tr>
<th>Ab Function</th>
<th>Target</th>
<th>Result</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opsonization</td>
<td>Platelet surface proteins</td>
<td>Splenic clearance</td>
<td>Drug-induced thrombocytopenia</td>
</tr>
<tr>
<td>Neutralization</td>
<td>Acetylcholine receptor</td>
<td>Receptor blocking</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>ADCC</td>
<td>Glomerular basement membrane proteins</td>
<td>Glomerular destruction</td>
<td>Post-Streptococcal renal failure</td>
</tr>
<tr>
<td>Complement-mediated lysis</td>
<td>Penicilloyl-RBC protein conjugates</td>
<td>RBC destruction</td>
<td>Drug-induced hemolytic anemia</td>
</tr>
<tr>
<td>Non-Physiologic</td>
<td>TSH receptor</td>
<td>Receptor activation</td>
<td>Grave’s disease</td>
</tr>
</tbody>
</table>

Type III Hypersensitivity: Immune Complex Disease

• First Description: Arthus Reaction
- Rabbit received an intravenous infusion of anti-toxin antibody
- Three days later, antigen (toxin) was injected subcutaneously
- Local erythema/tenderness with edema, necrosis, and hemorrhage developed within 8 hours = Arthus Reaction

**Type III Hypersensitivity: Clinical Manifestations**

• Serum Sickness:
  - Rash
  - Fever
  - Lymphadenopathy
  - Joint Pain
  - Proteinuria

2-3 wks. following infusion of a protein antigen (classically an anti-toxin anti-serum of horse origin)

**Immune Complex Formation**

Antibody-Antigen Equivalence

**Arthus Reaction**

• Immune Mechanism
- Antibody-Antigen complexes form within blood vessel walls
- Complement fixation generates C5a
- Neutrophil chemoattractant PMN infiltration
- Anaphylotoxin - local mast cell histamine release tissue edema
- 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

**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

<table>
<thead>
<tr>
<th>Internal anti-Ova Ab</th>
<th>+</th>
<th>+</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.V. Ova</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Genotype</td>
<td>C5aR+/+</td>
<td>C5aR−/−</td>
<td></td>
</tr>
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Importance of FcγRs in I.C. Disease

- B/W Mouse - spontaneous accumulation of I.C.’s in the glomerulus leads to early death from renal failure
- FcγRI and FcγRIII - contain ITAM’s; activating for phagocytes
- Lack of FcγRI/FcγRIII protects against I.C.-mediated glomerular damage, despite accumulation of IgG/C3b-containing immune complexes


Type IV (Delayed-Type) Hypersensitivity

- Group of related responses to antigen, all dependent on T cell-mediated immunity
- Prior sensitization is required
- Reactions occur over 1-3 days following re-exposure
- T cells: necessary and sufficient for DTH
  - Athymic subjects (animal or human) do not get DTH rens.
  - T cell depletion (via anti-T cell Ab’s) reverses sensitization
  - Transfer of purified memory T cells confers sensitization

Manifestations of DTH Reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Site</th>
<th>Clinical Appearance</th>
<th>Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact</td>
<td>Epidermis</td>
<td>Erythematous, Pustular, Scaling</td>
<td>Poison ivy, latex, organic mols., metals (Ni++)</td>
</tr>
<tr>
<td>Tuberculin</td>
<td>Dermis</td>
<td>Local Induration</td>
<td>Mycobacteria, Candida, Mumps</td>
</tr>
</tbody>
</table>

Common to all DTH Reactions

- Histology of the DTH reaction:
  - T Cells - CD4 (Th1); some forms CD8
  - Macrophages/monocytes
  - Basophils
  - Tissue edema with fibrin extravasation
  - 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 Hypersensitivity

A. Urushiol (P.I.)  B. Analine (dyes)  C. Chromates (leather tanning)

Contact Sensitivity: Hapten DTH

- Phase One: Initial Exposure - Sensitization
  - Antigen - typically a small organic hapten, frequently lipophilic
  - Exposure - crosses epidermal barrier by diffusion, associates with epidermal cell proteins (“haptenylation”)
  - Processing - haptenylated proteins are picked up by Langerhans cells ➔ peptides ➔ loaded onto MHC I and II
  - Presentation - loaded LC’s migrate to regional lymph nodes where they present haptenylated proteins to naive T cells
Contact Sensitivity: Hapten DTH

- 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) → CD4+ T cell activation → secretion of IFN-γ, MCP-1 → macrophage recruitment
    - Keratinocyte (MHC I) (lipophilic hapten) → CD8+ CTL activation → release of perforins and granzyme → local tissue damage

Hypersensitivity: Gell & Coombs Classification

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
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<tbody>
<tr>
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<td>IgE</td>
<td>IgG Monomer</td>
<td>IgG Multimers</td>
<td>CD4 T cell</td>
</tr>
<tr>
<td>Antigen</td>
<td>Soluble</td>
<td>Cell or Matrix Bound</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>Effector Mechanism</td>
<td>Mast Cell Activation</td>
<td>Complement FcR Cells</td>
<td>Complement</td>
<td>Macrophage</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Activation</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cytotoxicity (perforin/ granzyme)</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 0’ed risk of immediate (type I) hypersensitivity to local anesthetics (e.g., benzocaine) due to cross-reactivity of the aromatic core

Penicillin Mediates All Types

- 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>C3-mediated complement activation</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>