Hypersensitivity Mechanisms: An Overview

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Origins of Hypersensitivity

“Hypersensitivity” first used clinically in 1893:
• attempting to protect against diphtheria toxin
• test animals suffered enhanced responses, even death following second toxin exposure
• at miniscule doses not harmful to untreated animals

The term “Allergy” is coined in 1906:
• postulated to be the product of an “allergic” response
• from Greek allos ergos (altered reactivity)

First Task of the Immune System

Dangerous

?  

Innocuous

?
Modern Use

- Hypersensitivity:
  - Aberrant or excessive immune response to foreign antigens
  - Primary mediator is the adaptive immune system
    - T & B lymphocytes
  - Damage is mediated by the same attack mechanisms that mediate normal immune responses to pathogen
# Mechanisms of Hypersensitivity

## Gell & Coombs Classification

<table>
<thead>
<tr>
<th>G&amp;C Class</th>
<th>Common Term</th>
<th>Mediator</th>
<th>Example</th>
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<td>Type I</td>
<td>Immediate Type</td>
<td>IgE monomers</td>
<td>Anaphylaxis</td>
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<td>Type II</td>
<td>Cytotoxic Type</td>
<td>IgG/IgM monomers</td>
<td>Drug-induced hemolysis</td>
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<td>Type III</td>
<td>Immune Complex Type</td>
<td>IgG/IgM multimers</td>
<td>Serum sickness</td>
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<td>Type IV</td>
<td>Delayed Type</td>
<td>T cells</td>
<td>PPD rxn, Contact Dermatitis</td>
</tr>
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</table>
Common to All Types

Adaptive (T & B Cell) Immune Responses

• Reactions occur only in sensitized individuals
  • Generally at least one prior contact with the offending agent

• 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 (hapten)
Haptens

- **Definition:**
  - Chemical moiety too small to elicit a T cell response alone
  - Capable of tight association with self proteins
  - This “conjugation” creates a new (foreign) target

- **Example:**
  - Penicillin - capable of eliciting types I - IV hypersensitivity

[Diagram showing Hapten + Self → Modified Self]
Type I (Immediate) Hypersensitivity
Type I Hypersensitivity

• Sensitization
  • Antigen contact, typically low-dose via mucous membranes (respiratory, GI) \( \blacklozenge \) IgE production

• Elicitation (Re-exposure)
  • Pre-formed IgE (allergen-specific) triggers mast cell activation \( \blacklozenge \) mediator release

• Reactions
  • Can occur within seconds-minutes of exposure
  • Severity ranges from irritating to fatal
IgE Production

- Secondary immune response (multiple or persistent exposures)
- B cell class switch to IgE requires T cell help: CD40L and IL-4 or IL-13 (Th2 cytokines)
- 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
Sensitization Response

- IgE produced by plasma cells is rapidly taken up by FcεRI on tissue mast cells and circulating basophils (serum t½~2 days; compare to IgG~21 days)
Sensitization → Response

**Early Phase:** IgE crosslinking by antigen → release of

*preformed mediators*

**Immediate**
- Histamine (also tryptase, heparin)
- Smooth muscle constriction
- Vasodilatation; vascular leak
- G.I. motility (increased)
- Mucous Secretion
- Sensory nerve activation
Sensitization  △  Response

**Early Phase:** Followed by rapid production of arachadonic acid products

**Minutes**
- Leukotrienes, prostaglandins
- Smooth muscle constriction
- Vasodilatation; vascular leak
- Mucous Secretion
- Neutrophil chemotaxis
Sensitization △ Response

**Late Phase**: Gene activation △ new cytokine production

~6 hours after antigen triggering

**Cytokines**
- TNFα △ recruit inflammatory cells
- IL-3, IL-5, GM-CSF △ eosinophil production
- IL-4, IL-13 △ propagate Th2 response
**FcεRI Signaling**

- **Structure:** $\alpha\beta\gamma_2$
  - $\alpha$ - binds IgE monomer
  - $\gamma$ - shared by IgG FcR’s I & III

- **Receptor aggregation**
  - Pre-bound IgE binds polyvalent Ag
  - Initiates ITAM phosphorylation

- **ITAM’s**
  - Conserved tyrosine-containing sequence motifs within a variety of receptors (TCR, BCR, FcR’s)
Mast Cell Degranulation

Before

After
**Eosinophils**

- Innate responder cell in Type I hypersensitivity
- Production in bone marrow driven by:
  - IL-5 (Th2 cytokine); also IL-3 and GM-CSF
- Chemotaxis from blood to tissue sites utilizes:
  - IL-5
  - Eotaxins (CCL11, CCL24, and CCL26)
- Primed for activation by IL-5, eotaxins, C3a/C5a
  - ↑ Expression of FcR for IgG, IgA, IgE; also
Eosinophils (cont’d)

• **Activation:**
  - Most potent trigger is FcR-crosslinking (IgA > IgG > IgE)
  - Results in exocytosis of preformed toxic proteins
    - Major basic protein
    - Eosinophil cationic protein
    - Eosinophil-derived neurotoxin

• **Propogate the response:**
  - Secrete IL-3, IL-5, GM-CSF
  - Secrete IL-8 (PMN attractant)
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
  - ↑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) ⇒ ↑severity of schistosomal infection
<table>
<thead>
<tr>
<th>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><img src="image" alt="Allergens" /></td>
<td>Nasal Pruritis, Rhinorrhea, Congestion</td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
<td><img src="image" alt="Allergens" /></td>
<td>Bronchospasm, Chronic Airway Inflammation</td>
</tr>
<tr>
<td>G.I. Mucosa</td>
<td>Food Allergy</td>
<td><img src="image" alt="Allergens" /></td>
<td>Cramping/Colic, Vomit/Diarrhea, Eczema</td>
</tr>
<tr>
<td>Skin</td>
<td>Contact Urticaria</td>
<td><img src="image" alt="Allergens" /></td>
<td>Hives, Pruritis</td>
</tr>
<tr>
<td>Circulation</td>
<td>Anaphylaxis</td>
<td><img src="image" alt="Allergens" /></td>
<td>Hives, Laryngeal Edema, Hypotension</td>
</tr>
</tbody>
</table>
Anaphylaxis

• Response to systemic circulation of allergen
  • IgE cross-linking on mast cells in peri-vascular tissue
  • Circulating histamine, PG’s/LT’s ➟ vasodilatation, vascular leak
  • High-output shock: ↓↓BP despite ↑’ed cardiac output
  • Other symptoms: urticaria, wheeze, laryngeal edema with airway compromise, G.I. cramping, diarrhea, “feeling of dread”

• Symptoms progress rapidly (seconds)

• Treatment
  • Immediate: epinephrine 0.3 cc I.M., followed by antihistamines (H1 and H2 blockade) IM or IV
Demonstrating Type I Hypersensitivity

- Skin testing for allergic sensitization
  - Allergen (airborne, food, venom, medication) is introduced by prick or intradermal injection
  - Sensitization is evident with 15 minutes as a wheal/flare at site of allergen introduction

QuickTime™ and a decompressor are needed to see this picture.
Type II (Cytotoxic) Hypersensitivity
Type II Hypersensitivity

- Damage mediated by tissue-specific IgG or IgM
- Origins of tissue-specific antibody response
  - Hapten response
  - Molecular mimicry
  - Idiopathic - loss of self-tolerance (autoimmunity)
Hapten Response

- Mechanism of Sensitization
  - A foreign agent (typically drug) acts as a hapten
  - Conjugates self protein × modified self × T cell/B cell response × high-affinity anti-self IgG or IgM

- On re-exposure
  - Hapten conjugation to self × modified self protein
  - Binding of IgG or IgM to modified self tissue (platelet, RBC)
  - Activation of normal immunoglobulin effector
Molecular Mimicry

- Pathogen elicits appropriate inflammatory response
  - High-affinity anti-pathogen IgG
- Pathogen-specific antibody cross-reacts with self
- Long-lived anti-pathogen IgG persistent tissue damage
## Type II Hypersensitivity

<table>
<thead>
<tr>
<th>Ab Function</th>
<th>Target</th>
<th>Result</th>
<th>Syndrome</th>
</tr>
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<tr>
<td>Opsonization</td>
<td>Platelets</td>
<td>Splenic clearance</td>
<td>Drug-induced platelets bleeding</td>
</tr>
<tr>
<td>Complement Fixation</td>
<td>Erythrocytes</td>
<td>RBC destruction</td>
<td>Intravascular Hemolytic anemia</td>
</tr>
<tr>
<td>Antibody-Dependent Cellular Cytotoxicity</td>
<td>Cardiac myosin, perivascular connective tissue</td>
<td>Endocarditis, Myocarditis</td>
<td>Rheumatic Heart Disease</td>
</tr>
<tr>
<td>Neutralization</td>
<td>Acetylcholine Receptor</td>
<td>Muscle weakness</td>
<td>Myasthenia Gravis</td>
</tr>
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</table>
Type III (Immune Complex) Hypersensitivity
Type III Hypersensitivity

First Description: Arthus Reaction

- Another attempt at protection gone wrong:
  - IV infusion anti-toxin antiserum
  - Followed with SQ injection of small dose of toxin

- Outcome: local (cutaneous) erythema, swelling, hemorrhage and necrosis within 2
Immune Complex Formation

Increasing Antigen
Mechanism of Damage

- Ag-Ab complexes deposit in local blood vessel walls
- Fix complement $\nabla$ generate C5a
  - Chemoattractant for neutrophils
  - Mast cell activator $\nabla$ histamine release $\nabla$ hives, tissue edema
- Bind Fc Receptors on:
  - Neutrophils $\nabla$ release of $\mathbb{O}_2$ free radicals, proteases
  - Platelets $\nabla$ aggregation, thrombosis, necrosis
Clinical Type III Hypersensitivity

- Serum Sickness
- Fever
- Lymphadenopathy
- Urticaria
- Joint Pain
- Proteinuria

2-3 weeks following infusion of antigen (classically an anti-serum of horse origin)
Type IV (Delayed) Hypersensitivity
Type IV (Delayed) Hypersensitivity

• Group of T cell mediated responses to antigen
  • Direct killing of target cells (by CD8+ T cells)
  • Indirect via activation of macrophages (CD4+ T cells)

• Sensitization is required

• On re-exposure - reactions occur over 1-3 days

• T cells are necessary and sufficient
  • Athymic subjects do not have Type IV reactions
## Varieties of DTH Reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Site</th>
<th>Clinical Appearance</th>
<th>Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin Test</td>
<td>Dermis</td>
<td>Local Induration (swelling)</td>
<td>Mycobacteria, Candida, Mumps</td>
</tr>
<tr>
<td>Contact Dermatitis</td>
<td>Epidermis</td>
<td>Erythematous Papular</td>
<td>Poison ivy, latex, organic mols., metals (Ni++)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scaling Blistering</td>
<td></td>
</tr>
<tr>
<td>Drug Rash</td>
<td>Circulation</td>
<td>“Measles-like” rash, ↑LFT’s</td>
<td>Almost any medication</td>
</tr>
</tbody>
</table>
Contact Hypersensitivity: Sensitization

- Agent (antigen) crosses epidermis
  - If hapten, associates with epidermal cell proteins ≠ self
- Langerhans cells process antigen proteins
  - Load antigen peptides into MHC I and MHC II
- LC migration ≠ presentation to naïve T cells
Contact Hypersensitivity: Re-exposure

- If hapten modifies extracellular proteins, these will be taken up by cutaneous APC’s ➔ MHC II

- Effector CD4+ T cells respond:
  - Production interferon-γ, chemokines
  - Recruit macrophages ✗ produce TNF-α
  - Inflammatory infiltration, local edema/erythema

Analine (dyes) Chromates (leather tanning)
Contact Hypersensitivity: Re-exposure

- If lipophilic, the hapten easily crosses the cell membrane, modifying cytoplasmic proteins \( \rightarrow \) MHC I
- Effector CD8+ T cells respond:
  - Targeting of haptenylated keratinocytes for cytolysis
  - Keratinocyte death, blistering

Urushiols (Poison Ivy)
## Hypersensitivity: Overview

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
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<tbody>
<tr>
<td><strong>Example</strong></td>
<td>Immediate Hypersensitivity</td>
<td>Bystander Reaction</td>
<td>Immune Complex Disease</td>
<td>Delayed-type Hypersensitivity</td>
</tr>
<tr>
<td><strong>Mediator</strong></td>
<td>IgE</td>
<td>IgG Monomer</td>
<td>IgG Multimers</td>
<td>CD4 T cell</td>
</tr>
<tr>
<td><strong>Antigen</strong></td>
<td>Soluble</td>
<td>Cell or Matrix Bound</td>
<td>Soluble</td>
<td>Soluble, extracellular</td>
</tr>
<tr>
<td><strong>Effector Mechanism</strong></td>
<td>Mast Cell Activation</td>
<td>Complement, ADCC, Neutraliz., Opsonization</td>
<td>Complement, PMN, MΦ</td>
<td>Macrophage Activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cytotoxicity (perforin &amp; granzyme)</td>
</tr>
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