Hypersensitivity

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Definitions

- Hypersensitivity:
  - Aberrant or excessive immune response to foreign antigens
  - Primary mediator is the adaptive immune system (B & T cells)
  - Same effector mechanisms that mediate normal immune response
- Allergy:
  - Symptoms elicited by encounter with foreign antigen in a previously sensitized individual

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

Emil von Behring

The term "Allergy" is coined in 1906:

- postulated to be the product of an "allergic" response
- from Greek *allos ergos* (altered reactivity)

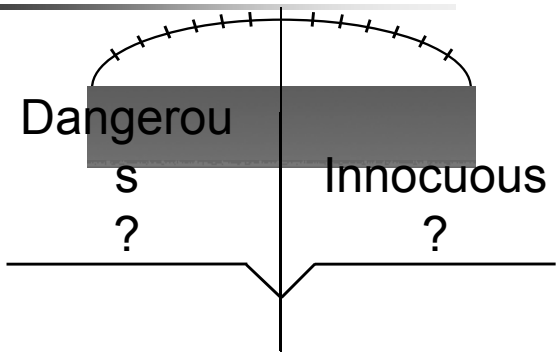
Clemens von Pirquet

Photos from Silverstein, AM. 1989. A History of Immunology. Academic Press, San Diego

Mechanisms of Hypersensitivity: Gell & Coombs Classification

G&C Class	Common Term	Mediator	Example
Type I	Immediate Hypersensitivity	IgE monomers	Anaphylaxis
Type II	Bystander Rxn	IgG monomers	Drug-induced hemolysis
Type III	Immune Complex Disease	IgG multimers	Serum sickness
Type IV	Delayed Hypersensitivity	T cells	PPD rxn

First Task of the Immune System



Common to All Types

Because the culprit is the adaptive immune system:

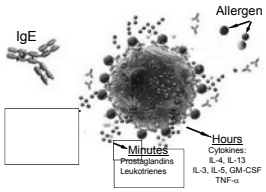
- Reactions occur only in sensitized individuals
- Sensitization requires contact with the offending agent
  - usually at least one prior exposure (exception, type III)
- Sensitization can be long lived in the absence of re-exposure (>10 years) due to immunologic memory
- Antigen is a protein or is capable of complexing with protein (e.g., nickel ion, penicillin)

Type I (Immediate) Hypersensitivity

- Antigens:
  - Exogenous, otherwise innocuous
  - Typically low dose exposure via mucous membranes (respiratory, GI)
- Immune Mechanism
  - Sensitization: antigen contact leads to IgE production
  - 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

Type I Rxn: Effector Stage

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

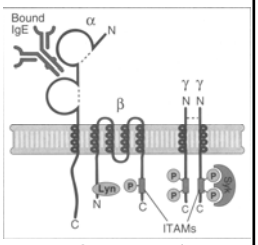


IgE Production

- By definition, a secondary immune response (multiple or persistent exposures)
- Class switch to IgE is directed by IL-4 and IL-13 (Th2), 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

$Fc\varepsilon RI$ Signaling

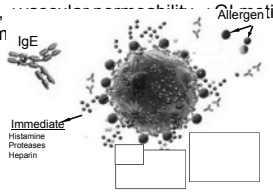
- Structure: $\alpha\beta\gamma_2$
  - Alpha- binds IgE monomer
  - Gamma- shared by IgG FcR's I & III
- Receptors are aggregated
  - When pre-bound IgE binds multivalent Ag
  - Initiates ITAM phosphorylation
- ITAM's
  - Conserved tyrosine-containing sequence motifs within a variety of receptors (TCR, BCR, FcR's)
  - Serve as docking sites for downstream activating kinases, in this case, Syk



Immunoreceptor
Tyrosine-based
Activation
Motif

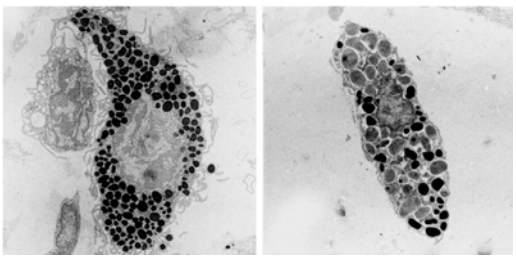
Type I Rxn: Effector Stage

- *Early Phase Response*: within seconds-minutes
  - IgE crosslinking by antigen ⇨ release of preformed mediators
  - Histamine ⇨ smooth muscle constriction, mucous secretion, [illegible] tility, sens. nerve stim



Mast Cell Degranulation

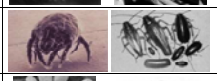
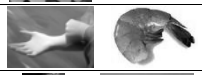
Before Ag exposure | After Ag exposure



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
  - ⇧expression of receptors for IgG, IgA, and complement
  - induce $Fc_{\varepsilon}R$ expression
  - ⇩threshold for degranulation

Manifestations of Type I Hypersensitivity

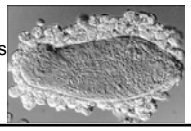
Exposure	Syndrome	Common Allergens	Symptoms
Respiratory Mucosa	Allergic Rhinitis		Nasal Pruritis Rhinorrhea Congestion
	Asthma		Bronchospasm Chronic Airway Inflammation
G.I. Mucosa	Food Allergy		Cramping/Colic Vomit/Diarrhea Eczema
Skin	Contact Urticaria		Hives Pruritis
Circulation	Systemic Allergy		Hives Laryngeal Edema Hypotension

Eosinophils

- Activation:
  - Most potent trigger is Ig-crosslinking (IgA>IgG>IgE)
  - Results in exocytosis of pre-formed eosinophil toxic proteins
- Anti-microbial effect:
  - major basic protein
  - eosinophil cationic protein
  - eosinophil-derived neurotoxin

  } Directly toxic to helminths

  Also cause tissue damage
- Propogate the response:
  - secrete IL-3, IL-5, GM-CSF (more eos
  - secrete IL-8 (PMN)



Anaphylaxis

- Response to systemic circulation of allergen
  - Triggering of 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 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*

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

Demonstrating Type I Hypersensitivity

Documenting allergic 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

- Antibody-mediated "Bystander Reactions"
  - Immune effector is a target-specific IgG (or IgM)
  - Result is damage to "innocent bystander" self tissues
- Definition: Haptens
  - Chemical moieties too small to elicit a T cell response alone
  - Capable of covalent conjugation to self proteins
  - Conjugation creates a new (non-self) target or epitope
    - the penicilloyl metabolite of penicillin reacts with lysine sidechains on host proteins
    - penicilloyl-protein conjugates represent *neoepitopes* - e.g., on the surface of an RBC or platelet

Type III Hypersensitivity: Immune Complex Disease

First Description: Arthus Reaction

- Rabbit received an intravenous infusion of anti-toxin antibody

- Three days later, received a subcutaneous injection of toxin
- Local erythema/tenderness with edema, necrosis, and hemorrhage developed within 8 hours = Arthus Reaction

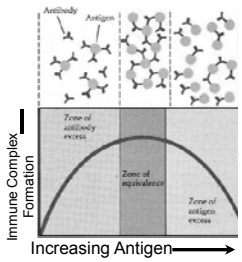
Type II Hypersensitivity: Ab Generation

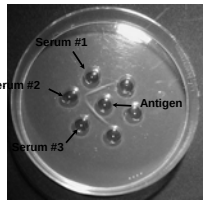
Mechanisms of sensitization:

1. Hapten Response
   A. Foreign agent (typically drug) acts as a *hapten* to elicit a tissue-specific antibody response
   B. The drug-induced antibody binds its target tissue and activates normal immunoglobulin effector functions, resulting in tissue damage
2. Molecular Mimicry
   A. Pathogen elicits an appropriate Ab response
   B. 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

Immune Complex Formation

Antibody-Antigen Equivalence



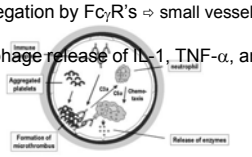


Mechanisms of Type II Hypersensitivity: Exactly those of normal Ab function (plus some):

Ab Function	Target	Result	Syndrome
O			
N			
A			
C			

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 ⇨ tissue edema
  - Neutrophil activation by $Fc_\gamma R$'s ⇨ release of cytotoxic enzymes
  - Platelet aggregation by $Fc_\gamma R$'s ⇨ small vessel thrombosis, necrosis
  - Local macrophage release of IL-1, TNF-α, and IL-8 ⇨ propagation

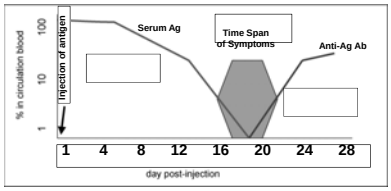


Type III Hypersensitivity: Clinical Manifestations

Serum Sickness:

- Rash, hives
- Fever
- Lymphadenopathy
- Joint Pain
- Proteinuria

} 2-3 weeks following infusion of antigen (classically an anti-toxin anti-serum of horse origin)



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)

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 rxns.
  - T cell depletion (via anti-T cell Ab's) reverses sensitization
  - Transfer of purified memory T cells confers sensitization

Contact Hypersensitivity

A. B. C. tanning)

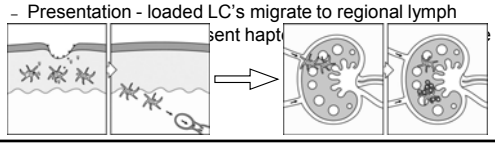
Manifestations of DTH Reactions

Type	Site	Clinical Appearance	Antigen
Contact Dermatitis	Epidermis	Erythematous Papular Scaling Blistering	Poison ivy, latex, organic mols., metals (Ni^{++})
Tuberculin	Dermis	Local Induration	Mycobacteria, Candida, Mumps

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 sent hapt



Contact Sensitivity: Hapten DTH

Phase Two: Re-exposure - Elicitation

- Hapten-specific memory T cells perform continuous surveillance migrating 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: Overview

	Type I	Type II	Type III	Type IV	
	Immediate Hyper-sensitivity	Bystander Reaction	Immune Complex Disease	Delayed-type Hypersensitivity	
	Peanut Anaphylaxis	PCN-assoc. Hemolysis	Serum Sickness	Contact Dermatitis (Ni^+), PPD	Contact Dermatitis (poison ivy)
	IgE	IgG Monomer	IgG Multimers	CD4 T cell	CD8 T cell
	Soluble	Cell or Matrix Bound	Soluble	Soluble	Cell Associated
	Mast Cell Activation	Complement, FcR^+ Cells	Complement, PMN, Mφ	Macrophage Activation	Cytotoxicity (perforin/ granzyme)

Summary

1. The phenomenon of hypersensitivity was recognized more than a century ago, long before our understanding of the adaptive immune system which drives it.
2. Gel & Coombs divided hypersensitivity syndromes into four types based on the underlying immune players. The first three represent antibody-associated mechanisms of tissue damage, while the fourth is cell-mediated.
3. Type I (or immediate) hypersensitivity can range from acute episodic reactions to chronic debilitating disease. Sensitization can be long lived even in the absence of re-exposure to the offending antigen.
4. Type II (or bystander) hypersensitivity represents damage resulting when the humoral immune system becomes directed against self. The tissue damage in type II hypersensitivity is mediated by normal antibody effector functions.
5. Type III (or immune complex) hypersensitivity results from the interaction of soluble antibodies with soluble antigen to form an insoluble aggregate which causes damage nonspecifically, typically to blood vessel walls, resulting in a serum sickness-like syndrome.
6. Type IV (delayed-type) hypersensitivity represents a T cell-mediated immune response and may be orchestrated by $CD4^+$ or $CD8^+$ T cells, depending on the nature of the target antigen.