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


Emil von Behring

- 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)


Clemens von Pirquet

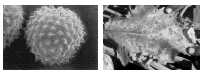
Photos from Silverstein, AM. 1989. A History of Immunology. Academic Press, San Diego

Definitions

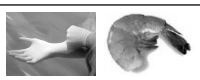
- Hypersensitivity:
  - Broadest (Abbas) - Disorders caused by immune responses
    - Dysregulated response to foreign antigen
    - Failure of tolerance to self-antigen
  - Practical - Used clinically to refer to aberrant or excessive immune responses generated against foreign antigens, although the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

Site of Exposure	Syndrome	Common Allergens	Symptoms
Respiratory Mucosa	Allergic Rhinitis		Nasal Pruritis Rhinorrhea Congestion
	Asthma		Bronchospasm Chronic Airway Inflammation
G.I. Mucosa	Food Allergy		Cramping Vomit/Diarrhea Hives Anaphylaxis

Manifestations of Hypersensitivity

Site of Exposure	Syndrome	Common Allergens	Symptoms
Skin	Contact Urticaria		Hives Pruritis
	Contact Dermatitis		Rash Pruritis
Blood	Systemic Allergy		Hives/Edema Abd. Cramping Bronchospasm Hypotension

Hypersensitivity: Gell & Coombs Classification

	Type I	Type II	Type III	Type IV	
Common Name	Immediate Hyper-sensitivity	Bystander Reaction	Immune Complex Disease	Delayed-type Hypersensitivity	
Example	Peanut Anaphylaxis	PCN-assoc. Hemolysis	Serum Sickness	Contact Dermatitis (Ni^+), PPD	Contact Dermatitis (poison ivy)
Mediator	IgE	IgG Monomer	IgG Multimers	CD4 T cell	CD8 T cell
Antigen	Soluble	Cell or Matrix Bound	Soluble	Soluble	Cell-associated
Effector Mechanism	Mast Cell Activation	Complement $Fc\gamma R^+$ Cells	Complement PMN, MΦ	Macrophage Activation	Cytotoxicity (perforin/ granzyme)

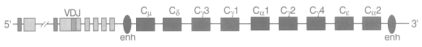
Common to All Types

- 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

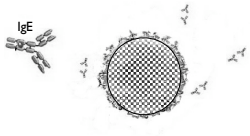
IgE Production



- 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

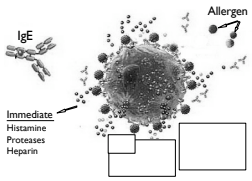
Type I Rxn: Sensitization Stage

- 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 $Fc_\varepsilon RI$ on tissue mast cells and circulating basophils



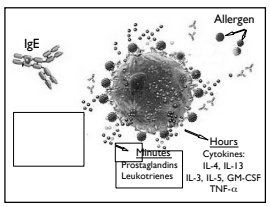
Type I Rxn: Effector Stage

- *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



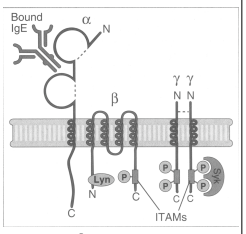
Type I Rxn: Effector Stage

- *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



$Fc_\varepsilon RI$ Signaling

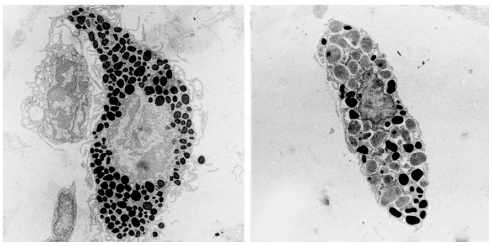
- Structure: $\alpha\beta\gamma_2$
  - Alpha- binds IgE monomer
  - Gamma- shared by IgG FcR's I & III
- Receptors are aggregated
  - When pre-bound IgE binds multivalent Ag
  - Initiates ITAM phosphorylation
- ITAM's
  - Conserved tyrosine-containing sequence motifs within a variety of receptors (TCR,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



Immunoreceptor **T**yrosine-based **A**ctivation **M**otif

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
  - ⇧$Fc_\gamma R$ & $Fc_\alpha R$ expression; ⇧C' receptor expression
  - induce $Fc_\varepsilon R$ expression
  - ⇩threshold for degranulation

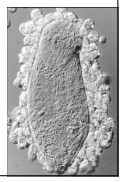
Eosinophils

- 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

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



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
    - Hx of measles or HAV infection, or +PPD ➡ ⇩allergy rates
    - 1990 - East/West Berlin immediately after the wall fell: East had
    - ⇩vaccination rates, ⇧prev. childhood infection, but ⇩'ed asthma

Allergy Epidemic

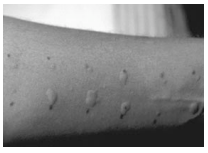
- Weighing against the Hygiene Hypothesis:
  - Despite this epidemiologic data, some evidence is hard to reconcile
    - Previous infection with helminths, which generates a strong Th2 response, is also associated with protection against allergy
    - Early life exposure to pathogens is also associated 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

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 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



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: 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 <u>early phase</u>
  - subsequent administration corticosteroids➟ prevent <u>late phase</u>

Type II Hypersensitivity

- Antibody-mediated "Bystander Reactions"
  - Immune effector is target-specific IgM and IgG
  - (Contrast with Type III Rxns 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

Type II Hypersensitivity

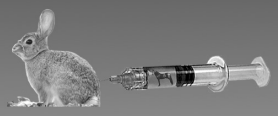
- Drug Reactions
  - Hapten - a molecule too small to elicit an immune response itself, but capable of covalent conjugation to self proteins, creating a new (non-self) target or epitope
    - example: penicillin is metabolized to yield the penicilloyl moiety which binds surface proteins on blood cells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

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

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

Type III Hypersensitivity: Immune Complex Disease

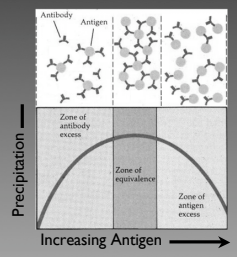
- First Description: Arthus Reaction
  - Rabbit received an intravenous infusion of anti-toxin antibody

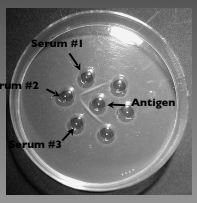


  - Three days later, antigen (toxin) was injected subcutaneously
  - Local erythema/tenderness with edema, necrosis, and hemorrhage developed within 8 hours = Arthus Reaction

Immune Complex Formation

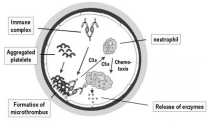
Antibody-Antigen Equivalence





Arthus Reaction

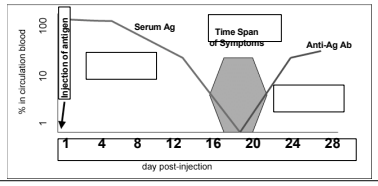
- Immune Mechanism
  - Antibody-Antigen complexes form within blood vessel walls
  - Complement fixation generates C5a
    - Neutrophil chemoattractant ➟ PMN infiltration
    - Anaphylatoxin - local mast cell histamine release ➟ tissue edema
  - Neutrophil activation by FcγR's ➟ release of cytotoxic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



Type III Hypersensitivity: Clinical Manifestations

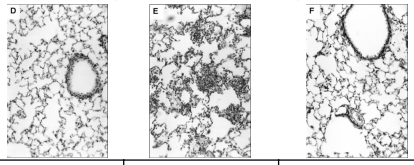
- Serum Sickness:
  - Rash
  - Fever
  - Lymphadenopathy
  - Joint Pain
  - Proteinuria

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



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

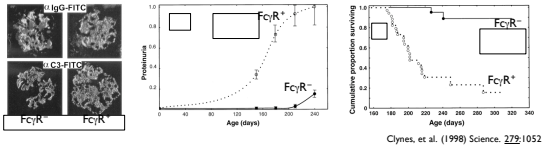


Intratracheal Anti-Ova Ab	+	+	+
I.V. Ova	–	+	+
Genotype	$C5aR^{+/+}$		$C5aR^{-/-}$

Bozic, et al. (1996) Science. 273:1722

Importance of $Fc_\gamma R$'s 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



Clynes, et al. (1998) Science. 279:1052

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

Manifestations of DTH Reactions

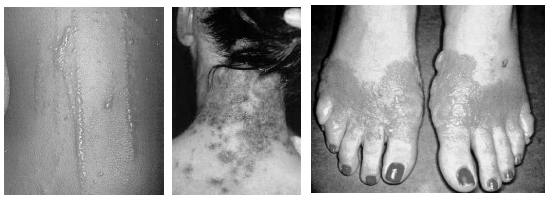
Type	Site	Clinical Appearance	Antigen
Contact	Epidermis	Erythematous Papular Scaling Blistering	Poison ivy, latex, organic mols., metals (Ni^{++})
Tuberculin	Dermis	Local Induration	Mycobacteria, Candida, Mumps

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)

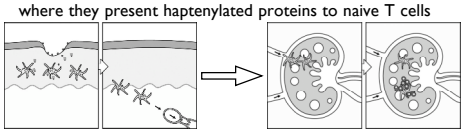
Contact Hypersensitivity

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

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Effector Mechanism	Mast Cell Activation	Complement FcR^+ Cells	Complement PMN, MΦ	Macrophage Activation	Cytotoxicity (perforin/ granzyme)

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 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 (!)

Type	Mechanism	Example
I	IgE-mediated	Acute anaphylaxis, Urticaria
II	C'-mediated cytolysis Opsonization	Hemolytic anemia Thrombocytopenia
III	Immune Complex Damage	Serum sickness Drug fever, Vasculitis
IV	T Cell mediated	Contact sensitivity