Hypersensitivity

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Timeline

- 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"

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"

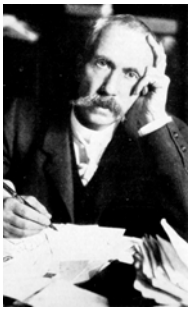
All historical photos from Silverstein, AM. 1989. A History of Immunology. Academic Press, San Diego

Timeline

- 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.

Timeline

- 1902 - Charles Richet and Paul Portier
  - Set sail on the yacht of the Prince of Monacco to study the effects of marine toxins in mammals
  - Attempted to protect dogs from the effects of toxins by innoculating 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"

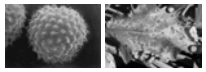


Definitions

- 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

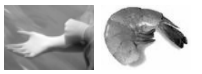
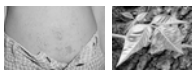
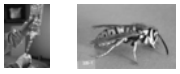
•Symptoms frequently are localized to the anatomical site of antigen exposure:

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

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

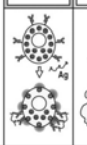
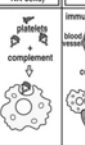
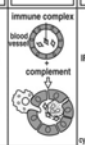
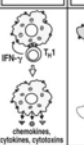
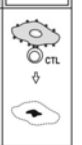
Manifestations of Hypersensitivity

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

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

Hypersensitivity: Gell & Coombs Classification

	Type I	Type II	Type III	Type IV	
Immune reactant	IgE	IgG	IgG	T_H1 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Complement, Phagocytes	Macrophage activation	Cytotoxicity
					
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (eg, penicillin)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Contact dermatitis

Immunobiology (Janeway), 6th Ed.

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

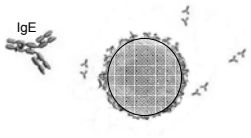
•"Atopic" individuals are those genetically predisposed to form IgE responses. That is, atopy is heritable

Genetics of Atopy

- Complex, multigenic heritability. Candidate genes:
  - Chrom. 11q - β-subunit of the high affinity $Fc_{\varepsilon}RI$
  - Chrom. 5q - Cytokine cluster: IL-3, IL-4, IL-5, IL-9, IL-13
  - TIM (T-cell, Ig domain, Mucin domain) - surface protein, variation assoc. with IL-4/IL-13 prod.
  - IL-12 p40 subunit (assoc. 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: Sensitization Phase

- Serum IgE produced by plasma cells has a short $T_{1/2}$ (serum $T_{1/2}$ IgG≈30 days; for IgE≈2 days)
- Rapidly taken up by $Fc_{\varepsilon}RI$ on tissue mast cells and circulating basophils

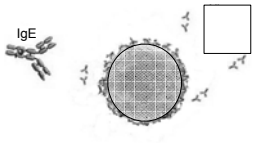


Allergy Epidemic

- 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: 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



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

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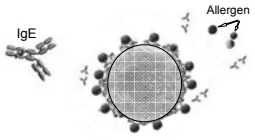

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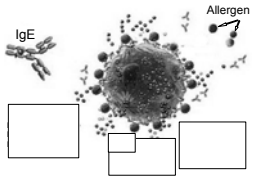


$Fc_{\varepsilon}RI$ Signaling

•Structure:

–Alpha, Beta, Gamma-Gamma

•Alpha - binds IgE monomer

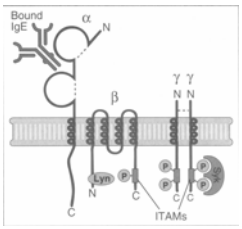
•Beta, Gamma - signal

•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

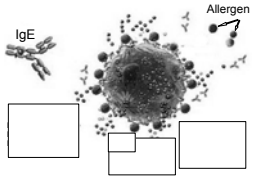


Allergy: Effector Phase

•*Late Phase Response*: 6-24 hours after exposure

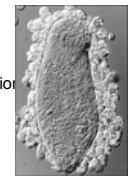
–Mast cell production of newly synthesized mediators

- –Leukotrienes → smooth mm. contraction, vasodil., chemotaxis
- –Cytokines → recruitment of PMN and eosinophils



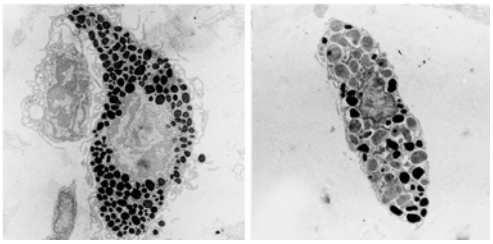
Eosinophils

- Innate responder cell in Type I hypersensitivity
  - Production in marrow induced by IL-3, IL-5, GM-CSF
  - Chemotax to tissue sites: IL-5, Eotaxin-1, 2, 3
  - "Primed" by IL-5, eotaxins, C5a
    - -↑$Fc_{\gamma}R$ and C' receptor expression
    - -induce $Fc_{\varepsilon}R$ expression
    - -↓threshold for degranulation
  - On activation, eosinophils secrete
    - -Toxic proteins- major basic protein, eos. catio
    - -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
  - ↑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

Evolutionary Role of Type I Response

•STAT6:

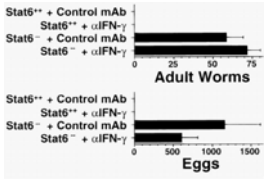
–Mediates IL-4/IL-13 signaling

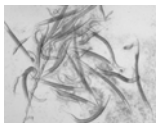
–Required for IgE class switch

–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





Urban, et al. (1998) Immunity. 8:255

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

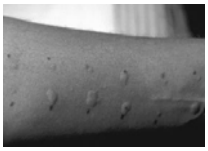
- Target-specific IgM and IgG mediate damage
- Targets:
  - Self-molecules altered by foreign antigen ⇗ neo-epitope
    - -penicillin conjugates to RBC surface proteins ⇗ new penicilloated-protein serves as a target for IgM/IgG ⇗ intravascular hemolysis
  - Self-molecules unaltered = breaking of tolerance
    - -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:

Ab Function	Target	Result
Opsonization	Platelet surface proteins	Splenic clearance, thrombocytopenia
Neutralization	Acetylcholine receptor	Myasthenia Gravis
ADCC	Glomerular basement membrane proteins	Goodpasteur's Disease
C' Fixation	Penicilloyl-RBC protein conjugates	Hemolytic anemia
Non-Physiologic	TSH receptor	Grave's Disease

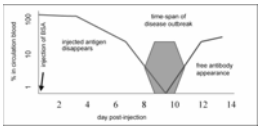
Type III Hypersensitivity: Immune Complex Mediated

- First Description: Arthus Reaction
  - (Arthus, N.M. 1903. Injections repetees de serum de cheval chez la lapin. C.R. Soc. Biol. (Paris) 55:817-820)
  - 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

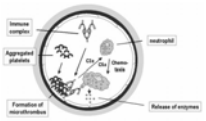
Type III Hypersensitivity: Immune Complex Mediated

- Serum Sickness: Systemic Arthus-like reaction
  - (Pirquet, C., von and B. Schick. 1905. Serum sickness. Franz Denticke, Leipzig)
    - Rash, fever, lymphadenopathy and arthralgias in recipients of anti-diphtheria antisera 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



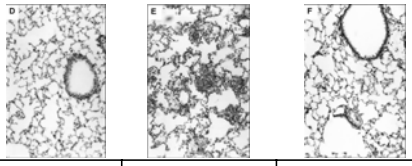
Arthus Reaction

- 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



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

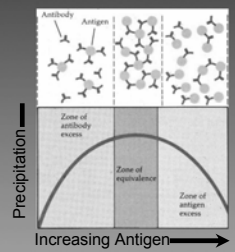


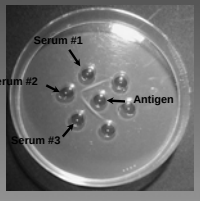
Intratracheal Anti-Ova Ab	+	+	+
I.V. Ova	–	+	+
Genotype	$C5aR^{+/+}$		$C5aR^{-/-}$

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

Immune Complex Formation

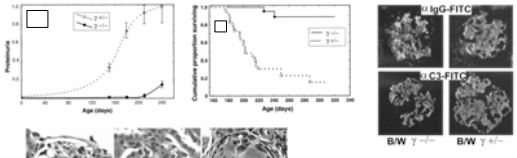
Antibody-Antigen Equivalence

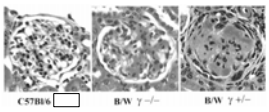




Importance of $Fc_\gamma R$'s in I.C. Disease

- B/W Mouse - spontaneous accumulation of I.C.'s in the glomerulus
- $Fc_\gamma RI$ and $Fc_\gamma RIII$ - contain ITAM's; activating for phagocytes
- γ-chain knockout ($\gamma^{-/-}$): Lacks expression of $Fc_\gamma RI$ and $Fc_\gamma RIII$





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

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
- Arthus reaction, serum sickness

transferrable with serum

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

Varieties of DTH Reactions

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

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

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

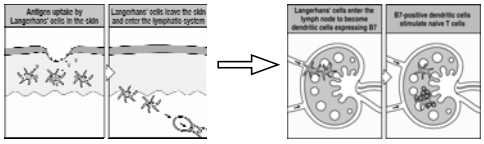
•Phase One: Initial Exposure - Sensitization

–Hapten - small organic molecule, frequently lipophilic crossing epidermal barrier by diffusion, associates with cell proteins

›–Chromates (leather tanning), urushiol (poison ivy), nickel

–Haptenylated 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



Penicillin Mediates All Types of Hypersensitivity

•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

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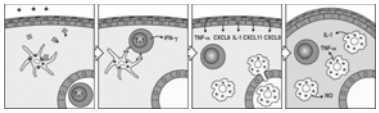
• Phase Two: Re-exposure - Elicitation

– 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



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 anesthetics (e.g., benzocaine) due to cross-reactivity of the aromatic core