

Allergies 4/18 & 4/20

Readings: Abbas pg. 193-207, Rosen Cases 36, 10, 37

Hypersensitivity disease: disorders caused by immune responses

May be caused by two types of abnormal immune responses:

1. responses to foreign antigens are uncontrolled, leading to tissue injury
2. failure of self-tolerance, leading to immune responses that are directed against self antigens

Hypersensitivity diseases are classified based on the immunologic mechanism responsible for tissue injury & disease

- **Immediate hypersensitivity** (aka type I): caused by release of mediators from mast cells.
-commonly triggered by production of IgE against environmental antigens & the subsequent binding of IgE to mast cells
- **Antibody-mediated** (aka type II): Antibodies (other than IgE) are directed against cell/tissue antigens that either damage the cell or impair its functions
- **Immune complex diseases** (aka type III): Antibodies against soluble antigens form complexes with these antigens, and these complexes often deposit in blood vessels/tissue, causing inflammation and tissue damage
- **T cell mediated** (aka type IV): caused by the reactions of T cells, often against self antigens

Immediate hypersensitivity (allergy, atopy): **rapid, IgE & mast cell mediated, mainly affecting smooth muscle & blood vessels**, often followed by inflammation, against foreign antigens previously exposed to.

Common types: food, hay fever, bronchial asthma, anaphylaxis

Steps in reaction:

1. production of IgE in response to antigen

-for some unknown reason, people who are prone to allergies mount strong T_H2 responses

-**IL-4 & IL-13** in particular, released by the T_H2 cells **stimulate B cells** (specific for foreign antigens) to **switch to IgE**

allergens: antigens that elicit immediate hypersensitivity

2. IgE binds to Fc receptors of mast cells

-mast cells are coated with IgE specific for the antigens to which the person is allergic (sensitization)

-the mast cells that are activated depends on the route of entry of the allergen

-IgE binds to a high affinity **Fcε receptor (FcεRI)** at one of its three chains, (the other two acting as signaling proteins)

3. cross-linking of IgE

-initial exposure to an allergen causes IgE production, a second exposure activates sensitized mast cells, which is the result of allergen binding to two or more IgE --> this causes cross-linking and signals the mast cell to degranulate, synthesize and secrete lipid mediators, and synthesize and secrete cytokines

4. **mast cell degranulation:** some mediators released cause immediate increase in permeability of blood vessels & smooth muscle contraction, while others recruit eosinophils and neutrophils to the site, causing inflammation --> this is the late phase reaction
- most important mediators: vasoactive amines & proteases released from granules, products of arachidonic acid metabolism & cytokines
- **histamine:** dilation of blood vessels, increased vascular permeability, transient contraction of smooth muscle
 - **proteases:** damage to local tissue
 - **arachidonic acid metabolites:** inc. prostaglandins: vascular dilation, leukotrienes: prolonged smooth muscle contraction
 - **cytokines:** inflammation, late phase reaction: mast cell-derived tumor necrosis factor & IL-4 promote neutrophil and eosinophil inflammation, increased leukocyte recruitment: eosinophils & neutrophils release proteases (cause tissue damage), T_H2 cells produce more cytokines

Clinical correlates & treatment:

Hay fever: (i.e. ragweed protein of pollen) mast cells in nasal mucosa produce histamine, causing increased mucus secretion, late phase reaction produces inflammation

---Treatment: desensitization by administering frequent low doses of allergens to (possible) inhibit IgE production, increase production of other Igs and induce T cell tolerance, anti-IgE, antihistamines, Cromolyn to inhibit mast cell degranulation

Food allergies: ingested allergens stimulate mast cell degranulation releasing histamine causing increased peristalsis

Bronchial asthma: inhaled allergens stimulate bronchial mast cells to release mediators that cause bronchial constriction and airway obstruction.

--Chronic asthma: large numbers of eosinophils, excessive mucus secretion causes bronchial smooth muscle to become hyper-reactive to allergens.

---Treatment: corticosteroids, phosphodiesterase inhibitors to reduce inflammation and relax bronchial smooth muscle

Anaphylaxis: edema, drop in blood pressure caused by widespread mast cell degranulation in response to systemic antigen.

---Treatment: epinephrine to contract smooth muscle, increase cardiac output and inhibit further mast cell degranulation

Antibody-mediated and Immune complex diseases

Usually, the antibodies are against **self antigens**, not foreign antigens

---example of antibody-mediated reaction against a foreign (here, microbial) antigen: late complications of streptococcal infections, i.e. antistreptococcal antibodies that cross-react w/antigens in heart muscle, causing rheumatic fever

Mechanism of action:

Antibodies against tissue antigens deposit in blood vessels, and cause inflammation by attracting leukocytes

IgG (esp. IgG1 & IgG3) bind to neutrophils and macrophages and activate the leukocytes

These IgG antibodies, and IgM activate the classical complement pathway, resulting in the recruitment of more leukocytes

Leukocytes activated at the site of antibody deposition produce reactive oxygen intermediates & lysosomal enzymes that damage tissue

Both Type II and Type III hypersensitivities are mediated by IgG (or occasionally IgM) antibody. Type II hypersensitivity results when antibody binds to cell surface antigen. The surface antigen-antibody complexes activate complement or bind to FcγRI on cells that can perform **antibody-dependent cell-mediated cytotoxicity (ADCC)**. Both processes result in lysis of the target cell.

Complement-mediated and ADCC-mediated lysis are normally directed against pathogens and are important protective mechanisms of the immune system. Classical complement activation by IgG releases inflammation-promoting anaphylatoxins and leads to formation of membrane attack complex (MAC) and lysis of the antibody-coated cell. Cells that mediate ADCC (K cells) include NK cells, neutrophils, eosinophils, and macrophages. K cells have FcγRI specific for antigen-bound IgG; they are not antigen specific. MHC is not involved in K cell recognition of ADCC targets. The cytotoxic mechanism depends on the particular K cell involved: NK cells use perforins, as they do for natural killing, while macrophages and granulocytes use proteases and toxic oxygen products.

Clinical examples of Type II hypersensitivities:

---**hyperacute graft rejection**: in which preformed antibodies to blood group antigens or transplantation antigens cause immediate, severe, and non-reversible damage to the graft

---**myasthenia gravis**: antibodies produced to the acetylcholine receptor

---**Graves' disease**: antibodies produced to the thyroid hormone receptor

Type II Hypersensitivities can be detected by **hemagglutination**.

Type III hypersensitivity is caused by immune complex deposition in the tissues, where the classical complement cascade results in tissue damage.

---Normally, numerous immune complexes too small to bind Fc receptors are removed from the circulation by erythrocytes bearing complement receptor CR1 before they can do any damage.

---often when antigen persists in the body for long periods or high levels of antigen are encountered at one time, immune complexes reach such high levels that they are no longer soluble.

---Common sites of deposition and tissue damage are blood vessel walls, kidney, and joints. Once cells are damaged and an inflammatory response is initiated, release of cytoplasmic enzymes and influx of inflammatory cells prolong the hypersensitivity.

A local inflammatory response (**Arthus reaction**) can be demonstrated in the skin of people with antibodies to the sensitizing antigen. Antigen injected into the skin binds antibody and the complexes bind FcγRII on skin mast cells. Release of mast cell mediators and complement activation result in local inflammation, with swelling and reddening at the injection site.

Clinical examples of Type III hypersensitivity:

---**serum sickness**: occurs in response to passive immunization with foreign antiserum after 7-10 days, enough IgG anti-(foreign thing) antibody has been produced to form immune complexes in the circulation that deposit in small vessels and activate complement and macrophages. On second exposure to horse antibodies, the patient would begin experiencing serum sickness within a couple of days since isotype switching to IgG had already occurred.

T cell-mediated hypersensitivity

- Most diseases caused by autoimmunity
- Tissue injury is caused by delayed-type hypersensitivity mediated by CD4 cells, or by lysis of host cells by CD8 cells.

Type IV hypersensitivity, also called **delayed-type hypersensitivity (DTH)** because it occurs 48-72 hours after antigen contact, is mediated by antigen-specific T_H1 cells and activated macrophages.

---seen in allergic reactions to poison ivy and metals, but the same reactions occur in normal immune responses against intracellular parasites.

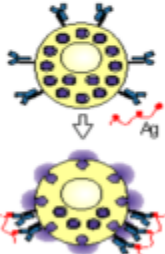
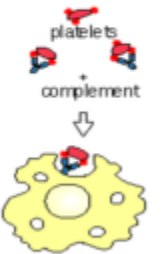
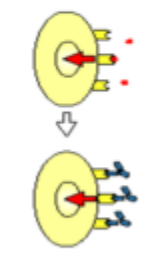
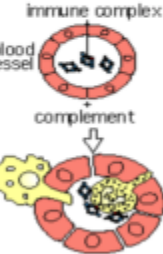
---T_H1 cells secrete chemokines to attract macrophages, IFNγ to activate macrophages, TNFα and TNFβ to upregulate adhesion molecules on local blood vessels, and IL-3 and GM-CSF to increase bone marrow output of monocytes. Although macrophages are not antigen specific, they are activated only in the vicinity of an antigen-activated T cell. Initial contact with antigen can produce memory T_H1 lymphocytes. As in Type I hypersensitivity, the initial response is called sensitization and may not result in symptoms.

Clinical examples:

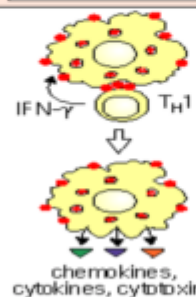
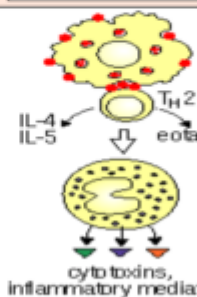
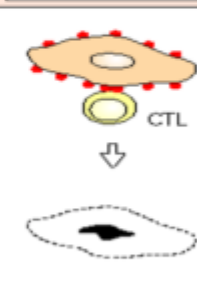
---**local skin reactions** to proteins in insect venom and injected Mycobacterial proteins used in skin testing

---**contact sensitivities to poison ivy, latex, nickel** in coins and jewelry, and cleaning products which come in contact with the skin. Small non-protein antigens either penetrate the skin or are scratched into the dermis in response to itching. They form complexes with skin proteins and peptides of the altered self proteins are taken up by Langerhans cells in the skin and migrate to regional lymph nodes to become dendritic cells. DC activate T_H1 cells or Tc cells and generate memory T cells that migrate to the skin. Second contact with antigen results in activation of memory T cells with IFNγ and IL-17 release. In response to

these cytokines, skin keratinocytes secrete IL-1, IL-6, TNF α , GM-CSF, and chemokines that attract macrophages and more T cells into the site for development of the characteristic itchy rash.

	Type I	Type II		Type III
Immune reactant	IgE	IgG		IgG
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen
Effector mechanism	Mast-cell activation	Complement, FcR ⁺ cells (phagocytes, NK cells)	Antibody alters signaling	Complement Phagocytes
				
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (eg penicillin)	Chronic urticaria (antibody to Fc ϵ R1 α)	Serum sickness, Arthus reaction

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	Type IV		
Immune reactant	TH1 cells	TH2 cells	CTL
Antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Macrophage activation	Eosinophil activation	Cytotoxicity
			
Example hypersensitivity reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Contact dermatitis

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An easy mini quiz:

1. Upon initial exposure to allergen, plasma cells secrete antigen-specific IgE that binds to mast cell Fc RI. The mast cells are said to be

- a. activated.
- b. allergenic.
- c. anaphylactic.
- d. sensitized.
- e. tolerized.

2. An immediate allergic mediator released by mast cells is

- a epinephrine.
- b IgE.
- c IL-4.
- d histamine.
- e prostaglandin.

3. Humans probably make IgE responses because

- a IgE binds more efficiently to low doses of antigen than IgG
- b IgE is protective against dangerous pollens.
- c IgE triggers eosinophils to release products toxic to helminth parasites
- d their T cells were not properly tolerized to self IgE in the thymus.
- e they cannot produce enough IgG to protect themselves against allergens.

4. All of the following are Type I hypersensitivities EXCEPT

- a an allergy to peanuts.
- b an anaphylactic reaction to bee stings.
- c a blood transfusion reaction.
- d asthma induced by cat dander.
- e hay fever.

5. Fran walks outside on a beautiful day and takes a deep breath of ragweed pollen, to which she has a strong Type I hypersensitivity. Which event below will NOT occur within 30 minutes due to this hypersensitivity?

- a. A local inflammatory response in the nose is induced, resulting in a runny or stuffy nose.
- b. IgE specific for ragweed pollen is synthesized by B cells in the local lymph nodes.
- c. Mast cells respond to the antigen-IgE signal by releasing preformed

histamine

d. Ragweed pollen antigen binds to IgE present on mast cell Fc RI in the respiratory tract.

e. Systemic effects of hypersensitivity such as anaphylactic shock may occur.

6. Type II hypersensitivities involve

a. anaphylactic shock.

b. complement-mediated lysis of antibody-coated cells.

c. cytotoxic T cell mediated lysis of antibody coated cells

d. chemotaxis of eosinophils.

e. IgE-mediated degranulation of mast cells.

7. All of the following are Type II hypersensitivities EXCEPT

a. a blood transfusion reaction to AB antigens on erythrocytes.

b. autoimmune hemolytic anemia, production of autoantibodies to erythrocyte antigens.

c. drug-induced hemolytic anemia, production of antibodies to medications which can bind to erythrocytes.

d. Grave's disease, production of autoantibodies to TSH receptor on thyroid cells.

e. serum sickness, production of antibodies to passively administered foreign antibodies.

8. Type II hypersensitivity results in all of the following EXCEPT

a. attraction and activation of inflammatory cells.

b. increased vascular permeability.

c. lysis of antibody coated cells by NK cells.

d. mediator release by CTL.

e. release of cytokines by macrophages.

9. A Type III hypersensitivity reaction is mediated by

a. antibody reacting with membrane antigen epitopes.

b. autoimmune reactions to self tissue antigens.

c. complement activation by immune complexes deposited in the blood vessel walls, kidneys, and joints.

d. cytokine release by Th1 cells.

e. the cell-mediated branch of the immune system.

10. As he cleared brush near his home, Frank was bitten by a rattlesnake. He went to the emergency room for treatment with horse IgG anti-rattlesnake venom. About a week after

the treatment, Frank experienced a rash, fever, swollen lymph nodes, and pains in his joints, all symptoms of serum sickness. These symptoms are probably due to

- a. a T cell memory response to horse IgG.
 - b. cross reactivity between horse IgG and human IgG.
 - c. late phase damage caused by the rattlesnake venom
 - d. production of IgG anti-horse immunoglobulin, which triggered a Type III hypersensitivity.
 - e. production of IgG anti-rattlesnake venom, which triggered a Type III hypersensitivity.
11. In the situation described in Question 10 above, Frank can be treated with
- a. antiserum to complement to block its activation.
 - b. human anti-horse IgG to more quickly clear the horse antibody.
 - c. immunosuppressive drugs to block B cell production of antibody.
 - d. plasmapheresis to remove antigen-antibody complexes from the blood.
 - e. rattlesnake venom to absorb the horse anti-venom antibody.
12. Type IV hypersensitivity (DTH)
- a. can be passively transferred with CD4 T cells.
 - b. causes chicken pox.
 - c. involves cell damage induced by IgG antibodies which are produced late in an immune response.
 - d. is mediated by memory macrophages.
 - e. occurs 1-2 weeks after antigen exposure.
13. During Delayed Type Hypersensitivity reactions, macrophages
- a. are not antigen specific.
 - b. are stimulated by IFN .
 - c. do not depend on antibody for antigen recognition.
 - d. kill neighboring cells, whether infected or not.
 - e. all of the above are true.
14. A positive skin reaction to tuberculin means that one has
- a. an active case of tuberculosis.
 - b. an allergy to *Mycobacterium tuberculosis*.
 - c. antibodies specific for *M. tuberculosis*.
 - d. macrophages containing *M. tuberculosis* in their phagolysosomes.
 - e. memory CD4 T cells specific for *M. tuberculosis*.
15. A common feature of all hypersensitivities is

- a. activation of CTL.
- b. activation of Th2 cells.
- c. antibody synthesis.
- d. inflammation.
- e. all of the above.

Answers:

- 1. d
- 2. d
- 3. c
- 4. c
- 5. b
- 6. b
- 7. e
- 8. d
- 9. c
- 10. d
- 11. d
- 12. a
- 13. e
- 14. e
- 15. d

If I made any mistakes or you have any questions, send me an e-mail at slam9@uiuc.edu. :)