Cell-Mediated Effector Responses

- Cytotoxic effector cells include the CD8 cytotoxic T cells of the adaptive immune system, NKT lymphocytes, which bridge the innate and adaptive immune systems, and NK cells, which were once associated strictly with the innate immune system but share intriguing functional features with their adaptive immune lymphocyte relatives.
- CTL, NKT, and NK effectors all induce cell death by triggering apoptosis in their target cells. Not only do these cytotoxic cells eliminate targets infected with intracellular pathogens (virus and bacteria), but they also play a critical role in eliminating tumor cells and cells that have been stressed by extreme temperatures or trauma.
- NK cells also play a less desirable role in rejecting cells from allogeneic organ transplants.
- Essentially, the cell-mediated immune response is prepared to recognize and attack any cell that exhibits “non-self ” or “altered-self ” characteristic

TENTH LECTURE

Granzyme and Perforin Mediated Cytolysis

- Many CTLs initiate killing of their targets via the delivery of pro apoptotic molecules. These molecules are packaged within granules their contents revealed 65-kDa monomers of a pore-forming protein called perforin and several serine proteases called granzymes (fragmentins).
- Almost immediately after conjugate formation, CTL granules containing granzyme and perforin are brought to the site of interaction between a killer and target
- Perforin internalized at the same time then forms pores that release granzyme B from the vesicle into the cytoplasm of the target cell.
- Regardless of the mechanism of entry, once in the cytoplasm،granzyme initiates a cascade of reactions that result in the fragmentation of the target-cell DNA into oligomers of 200 base pairs (bp); this type of DNA fragmentation is typical of apoptosis.

How CTLs Kill Cells

- A CTL can kill a target in two major ways: either via the directional release of granule contents or via a Fas-FasL membrane signaling interaction. Rather than inducing cell lysis, both of these processes induce the target cell undergo apoptosis, typically within a few hours of contact with the cytotoxic cell .
- CTL killing involves a carefully orchestrated sequence of events that begins when the attacking cell binds to the target cell and forms a cell-cell conjugate, an event so intimate that it is sometimes referred to as the “kiss of death.”
- Formation of a CTL-target cell conjugate is followed within several minutes by a Ca2-dependent, energy requiring step in which, ultimately, the CTL induces death of the target cell
- The CTL then dissociates from the target cell and goes on to bind another target cell.

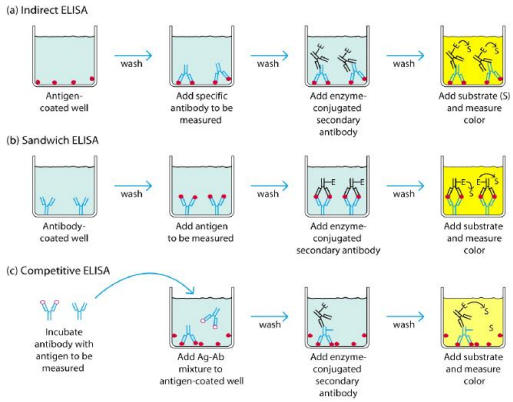
There are two types of antigen –antibody reactions

Primary antigen antibody reactions occur when individual antigenic determinants bind to appropriate antibody combining sites .

Secondary antigen antibody reactions involve the combination of an antigenic determinant and a antibody combining sites followed by aggregation of antigen – antibody complexes into macroscopically visible precipitates or clumps

Fas-FasL Mediated Cytolysis

Some potent CTL lines have been shown to lack perforin and granzymes. In these cases،cytotoxicity is mediated by Fas(CD95).This transmembrane protein, which is a member of the TNF-receptor family, can deliver a death signal when cross linked by its natural ligand, a member of the tumor necrosis factor family called Fas ligand (FasL). FasL is found on the membrane of CTLs, and the interaction of FasL with Fas on a target cell triggers apoptosis.



Many methods have been developed to assess primary antigen- antibody reactions . They include :

1- Radioimmunoassay (RIA)
2- Immunofluorescent assay (IFA)
3- Western blotting or (immunobotting)
4- Flow cytometry
5- Enzyme- linked immunosorbent assay (ELISA)

Hypersensitivity

- **In the early twentieth century, Richet coined the term "*anaphylaxis* ," derived from the Greek "against protection" to describe this overreaction of the immune system, the first description of a hypersensitivity reaction.**

- **The term allergy first appeared in the medical literature in 1906, that the response to some antigens resulted in damage to the host, rather than in a protective response.**

Secondary immune reactions

There are two types of secondary antigen-antibody reactions :

1. **Precipitation** is the term for the aggregation of soluble test antigens or precipitation is the combination of soluble antigen with soluble antibody to produce a visible insoluble complex. Precipitation reactions can occur in gels like :

A. Single radial imunodiffusion (SRID) or Mancini test

B. Double immunodiffusion or Ouchterlony test

2. Agglutination

Agglutination is the process whereby specific or particulate antigen (e.g., red blood cells) aggregate to form larger visible clumps when the corresponding specific antibody is present in serum.

TYPES OF HYPERSENSITIVITY REACTIONS

Type I or IMMEDIATE HYPERSENSITIVITY (anaphylactic)

- **Immediate hypersensitivity is an IgE antibody– and mast cell–mediated reaction to certain antigens that causes rapid vascular leakage and mucosal secretions, often followed by inflammation.**

- IgE-mediated immediate hypersensitivity reactions are also called **allergy,** or **atopy,** and individuals with a strong propensity to develop these reactions are said to be atopic.

- Such reactions may affect various tissues and may be of varying severity in different individuals.

- Common types of these reactions include hay fever, food allergies, bronchial asthma, and anaphylaxis.

- Allergies are the most frequent disorders of the immune system, estimated to affect about 20% of people and the incidence of allergic diseases has been increasing in industrialized societies.

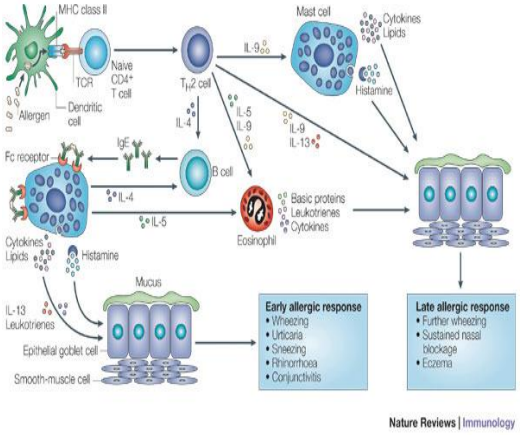
Classification

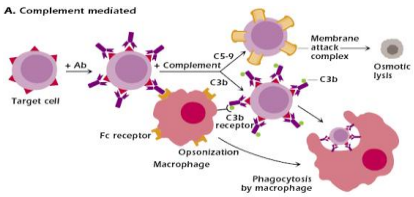
- **Coombs and Gell classification**

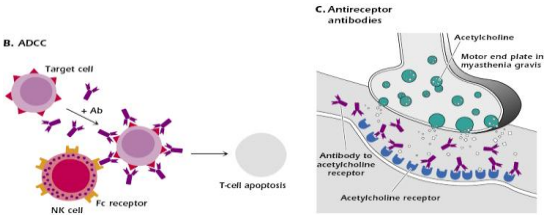
1-Type I - immediate (atopic, or anaphylactic)
2-Type II - antibody-dependent
3-Type III - immune complex
4-Type IV - cell-mediated or delayed

TABLE 15-1 Common allergens associated with type I hypersensitivity

Plant pollens	Foods
Rye grass	Nuts
Ragweed	Seafood
Timothy grass	Eggs
Birch trees	Peas, Beans
Drugs	Milk
Penicillin	
Sulfonamides	**Insect products**
Local anesthetics	Bee venom
Salicylates	Wasp venom
	Ant venom
Mold spores	Cockroach calyx
Animal hair and dander	Dust mites
Latex	
Foreign serum	
Vaccines	

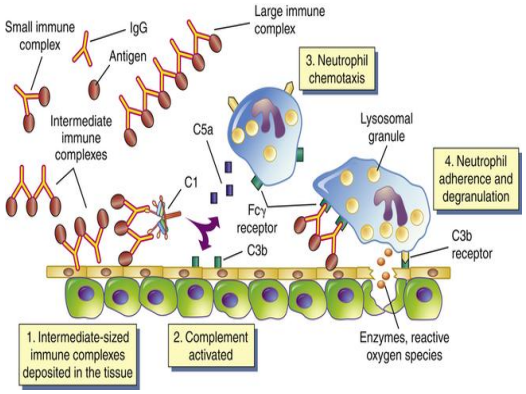






Antibody-Mediated (Type II) Hypersensitivity Reactions

- Type II hypersensitivity reactions involve antibody-mediated destruction of cells by immunoglobulins other than IgE. Antibody bound to a cell-surface antigen can induce death of the antibody-bound cell by three distinct mechanisms .
- First, certain immunoglobulin subclasses can activate the complement system, creating pores in the membrane of a foreign cell.
- Secondly, antibodies can mediate cell destruction by *a*ntibody *d*ependent cell mediated *c*ytotoxicity (ADCC), in which cytotoxic cells bearing Fc receptors bind to the Fc region of antibodies on target cells and promote killing of the cells.
- Finally, antibody bound to a foreign cell also can serve as an opsonin, enabling phagocytic cells with Fc or C3b receptors to bind and phagocytose the antibody-coated cell.
- Transfusion Reactions Are an Example of Type II Hypersensitivity Several proteins and glycoproteins on the membrane of red blood cells are encoded by genes with several allelic forms.



Type III or Immune complexes hypersensitivity

■ Immune complexes of antibody (IgG) and antigen can cause type III hypersensitivities when they cannot be cleared by phagocytes. This may be due to peculiarities of the antigen itself, or disorders in phagocytic machinery.

Immune Complex Disease

- Large amount of antigen and antibodies form complexes in blood.

If not eliminated can deposit in capillaries or joints and trigger inflammation.

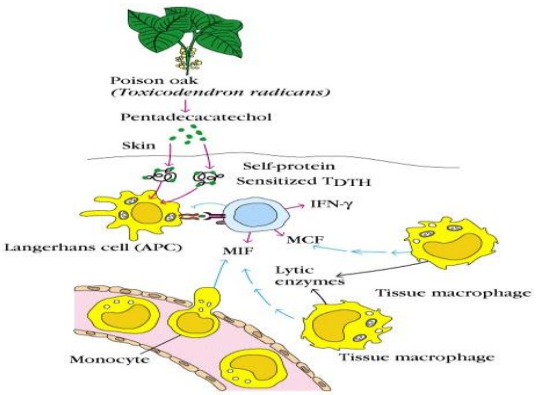
PMNs and macrophages bind to immune complexes via FcR and phagocytize the complexes.

BUT

If unable to phagocytize the immune complexes can cause inflammation via C' activation ---> C3a C4a, C5a and "frustrated phagocytes".

If neutrophils and macrophages are unable to phagocytize the immune complexes these cells will degranulate in the area of immune complex deposition and trigger inflammation

■ Arthus reactions are examples of immune complex (type III) hypersensitivity reactions and can be induced by insect bites, as well as inhalation of fungal or animal protein. They are characterized by local and sometimes severe inflammation of blood vessels.



Delayed-type hypersensitivity (type IV hypersensitivity)

■ Delayed-type hypersensitivity (type IV hypersensitivity) is cell mediated, not antibody mediated.

Examples include contact dermatitis caused by poison ivy, as well as the tuberculin reaction. DTH responses are responsible for granulomas associated with tuberculosis.

■ DTH requires T cells to be sensitized to antigen. Subsequent re-exposure to antigen results in cytokine generation, inflammation, and the recruitment of macrophages,which produce DTH symptoms 2 to 4 days after re-exposure.

■ T H 1 cells are classically associated with DTH, but other helper cell subsets have also been implicated recently like TH2 and T cytotoxic

Autoimmunity and Tolerance

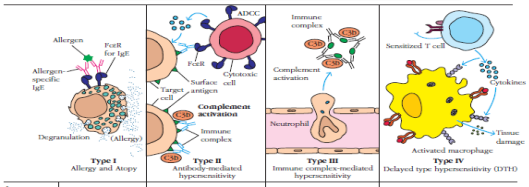
Tolerance : means the unresponsiveness to self antigen .

There are two types of tolerance

1. Central tolerance which occur in primary lymphoid organ
2. Peripheral tolerance which occur in secondary lymphoid organ

Failure of tolerance lead to occurrence of state called **autoimmunity** or the response to self antigen which cause autoimmune diseases

Allergy, Hypersensitivities



Immune mediator	IgE	IgG or IgM	Immune complexes	T cells
Mechanism	Ag induces cross-linking of IgE bound to mast cells and basophils with release of vasoactive mediators.	Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC.	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils.	Sensitized T cells (T_H1, T_H2 and others) release cytokines that activate macrophages or T_C cells which mediate direct cellular damage.
Typical manifestations	Includes systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema.	Includes blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia.	Includes localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.	Includes contact dermatitis, tubercular lesions, and graft rejection.

FIGURE 15-1 The four types of hypersensitivity reactions.

Immunodeficiency Disorders

- When the system errs by failing to protect the host from disease causing agents, the result is **immunodeficiency**.
- Immunodeficiency resulting from an inherited genetic or developmental defect in the immune system is called a **primary immunodefi ciency**.
- In such a condition, the defect is present at birth, although it may not manifest until later in life. These diseases can be caused by defects in virtually any gene involved in immune development or function, innate or adaptive, humoral or cell mediated,
- **Secondary immunodefi ciency**, also known as acquired immunodeficiency, is the loss of immune function that results from exposure to an external agent, often an infection. Although several external factors can affect immune function, by far the most well-known secondary immunodeficiency is ***a*cquired *i*mmuno*d*eficiency *s*yndrome (AIDS)**, which results from infection with the **human immunodeficiency virus(HIV)**.

TABLE 16-1 Some autoimmune diseases in humans

Disease	Self antigen/Target gene	Immune effector
ORGAN-SPECIFIC AUTOIMMUNE DISEASES		
Addison's disease	Adrenal cells	Auto-antibodies
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies
SYSTEMIC AUTOIMMUNE DISEASES		
Ankylosing spondylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T_H1 cells and T_C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes

Transplantation Immunology

Graft Rejection Occurs Based on Immunologic Principles

The degree and type of immune response to a transplant varies with the type and source of the grafted tissue. The following terms denote different types of transplants:

• **Autograft** is self tissue transferred from one body site to another in the same individual. Examples include transferring healthy skin to a burned area in burn patients and using healthy blood vessels to replace blocked coronary arteries.

• **Isograft** is tissue transferred between genetically identical individuals. This occurs in inbred strains of mice or identical human twins, when the donor and recipient are syngeneic.

• **Allograft** is tissue transferred between genetically different members of the same species. In mice this means transferring tissue from one strain to another, and in humans this occurs in transplants in which the donor and recipient are not genetically identical (the majority of cases).

• **Xenograft** is tissue transferred between different species (e.g., the graft of a baboon heart into a human). Because of significant shortages of donated organs, raising animals for the specific purpose of serving as organ donors for humans is under serious consideration.