Immunopathology

The chief role of the immune system is to **protect the host from invasion by foreign agents**. Immune responses can be elicited by a wide range of agents including toxins, drugs, chemicals, viruses, bacteria, parasites and transplanted foreign tissues.

Immune system include-

A-innate Immune system (non-antigen specific)**:-**

1-physical barriers such as (1) regionally adapted epithelia (e.g., thick skin, ciliated respiratory epithelium and a nearly impervious urothelium),(2) chemical–mechanical barriers (e.g., antibacterial lipids and mucus) (3) indigenous microbial flora that compete with potential pathogens.

2-Patterned hemodynamic responses, cell surface–associated and soluble mediator systems (e.g., complement and coagulation systems).

3-Non–antigen-specific phagocytes (e.g., resident macrophages, neutrophils).

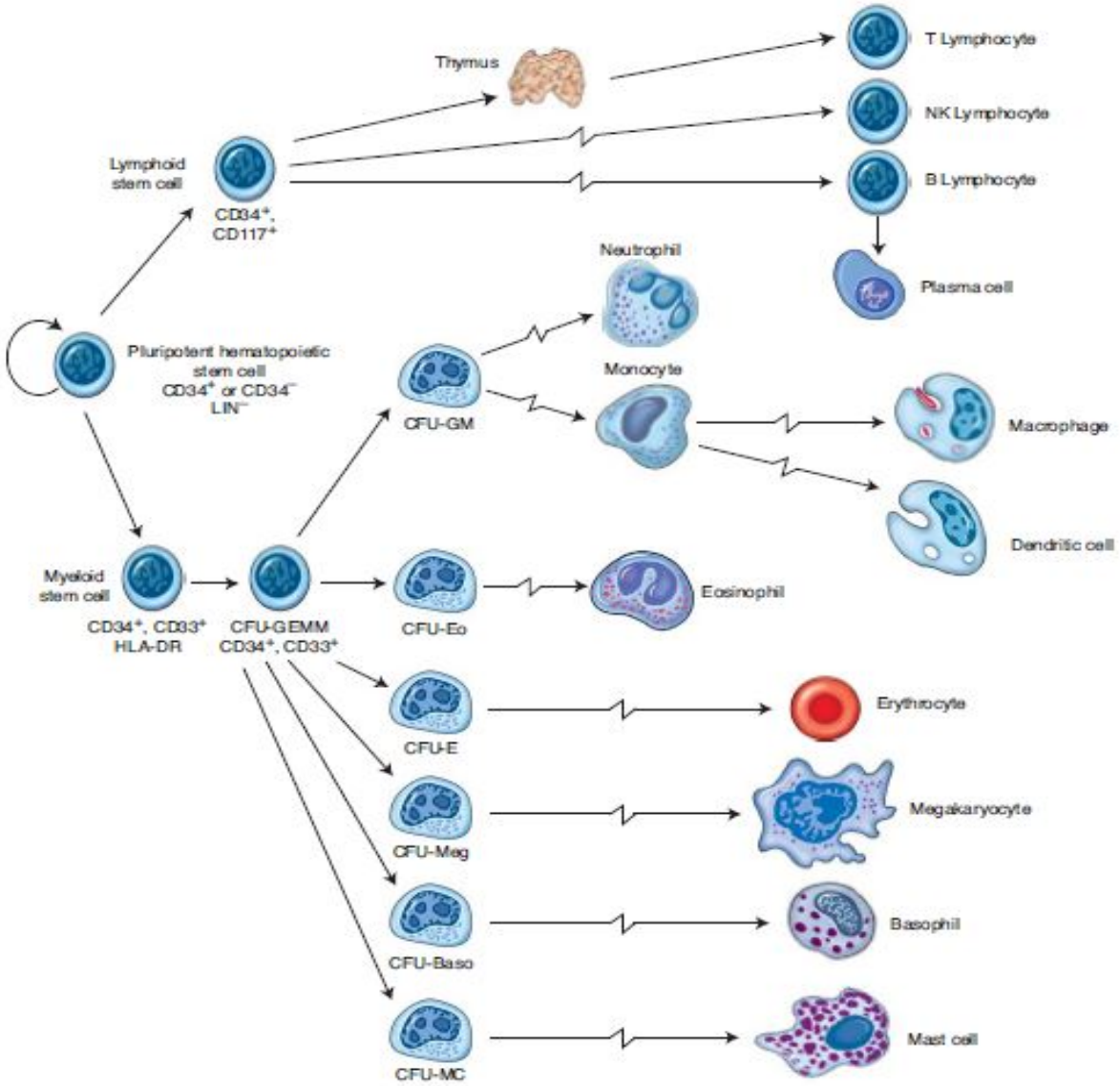
B- Adaptive Immune system (antigen-specific)**:-**

Encompasses lymphocytes, plasma cells, antigenpresenting cells (APCs), specific effector molecules (e.g., immunoglobulins) and a vast array of regulatory mediators. The defining features of adaptive immunity include **specificity**, **memory** and the **capacity for amplification**.

***The Cells That Comprise the Immune System Derive From Hematopoietic Stem Cells (HSCs)**

Near the end of the first month of embryogenesis, HSCs appear in the extraembryonic erythropoietic islands adjacent to the yolk sac. At 6 weeks, the primary site of hematopoiesis shifts from extraembryonic blood islands to fetal liver and then to bone marrow. The latter process begins at 2 months and by 6 months has completely shifted to bone marrow. Although there are well-defined sequential changes in the primary site of hematopoiesis, there are periods of overlap. By 8 weeks of gestation, lymphoid progenitors derived from HSCs that are

fated to become T cells circulate to the thymus where they differentiate into mature T lymphocytes. Lymphoid progenitors destined to become B cells differentiate first within fetal liver (8 weeks) and later within bone marrow (12 weeks).



Pluripotent hematopoietic stem cells differentiate into either lymphoid or myeloid stem cells and, in the case of myeloid stem cells, into lineage-specific colony-forming units (CFUs). Under the influence of an appropriate microenvironment, CFUs give rise to definitive cell types. Lymphoid progenitors are precursors of natural killer (NK) cells, T lymphocytes, and B lymphocytes. B lymphocytes give rise to plasma cells. Lin- _ lineage-negative; CD _ cluster designation; CFU-GEMM _ granulocytic, erythroid, monocytic–dendritic, and megakaryocytic colony-forming units; HLA _ human leukocyte antigen.

***Biology of the Immune System:-**

-Cellular Components of the Immune System:-

1-Lymphocytes:

***T Lymphocytes** CD4+, CD8- T cells function as helper cells, whereas most CD4-, CD8+ T cells serve as cytotoxic cells.

***B Lymphocytes** differentiate in the bone marrow into antibody secreting plasma cells B lymphocytes express a surface antigen-binding receptor, **membrane immunoglobulin** (mIg), with the same antigen-binding specificity as the soluble immunoglobulin that will ultimately be secreted by the corresponding terminally differentiated plasma cells. Like T cells, B lymphocytes also exhibit a degree of heterogeneity (e.g., CD5_ [B]) and CD5_ [B2]).

*** NK cells** recognize target cells mainly via antigen-independent mechanisms. NK cells bear several types of class I MHC molecule receptors, which when engaged actually *inhibit* the NK cell's capacity to secrete cytolytic products. Certain tumor cells and virus-infected cells bear reduced numbers of MHC class I molecules and thus do not inhibit NK cells.

2-Mononuclear Phagocytes, Antigen-Presenting Cells and Dendritic Cells:-

Mononuclear phagocytes, chiefly **monocytes**, account for 10% of circulating white blood cells. Circulating monocytes give rise to resident tissue macrophages including, among others, Monocytes and macrophages express an array of specific cell surface molecules that are important for their host defense functions. These include **MHC class II** molecules, **CD14** (a receptor that binds bacterial lipopolysaccharide and can trigger cell activation),

Activated macrophages produce a variety of **cytokines** and **soluble mediators** of host defense (e.g., interferon-_ [IFN-_], interleukin [IL]-1, tumor necrosis factor [TNF-] and complement components).

Antigen-presenting cells, defined by their function and derived from hematopoietic stem cells (HSCs), acquire the capacity to present antigen to T lymphocytes in the context of histocompatibility, after cytokine-driven upregulation of MHC class II molecules

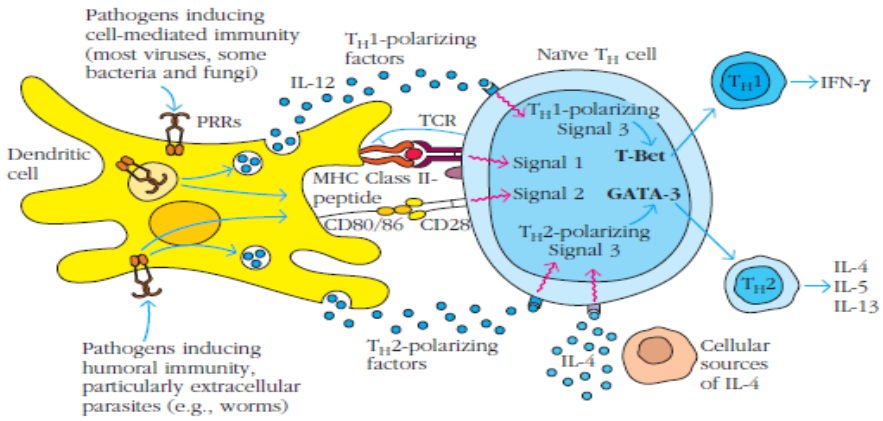


FIGURE 11-9 Regulation of T_H1 and T_H2 subset differentiation. This figure depicts some of the cellular events that drive T_H1 and T_H2 lineage commitment in more detail. Intracellular pathogens activate a cascade of signals that polarize cells to the T_H1 lineage. For example, viruses interact with PRRs (e.g., TLR-3) that induce dendritic cells to generate IL-12. This binds to receptors on naïve T cells, activating a signal transduction pathway mediated by STAT4 that induces expression of the transcription factor T-Bet. T-Bet, in turn, activates expression of effector cytokines, including IFN-γ, which define the T_H1 subset's functional capacities (and can also enhance T_H1 polarization). On the other hand, extracellular pathogens activate signal cascades that can polarize naïve T cells to the T_H2 lineage. Parasitic worms interact with PRRs on neighboring immune cells (such as mast cells, basophils, or germinal center B cells), triggering the release of the signature T_H2 polarizing cytokine IL-4. This interacts with receptors on T cells that activate STAT6, up-regulating expression of the transcriptional regulator GATA-3. GATA-3, in turn, induces expression of the T_H2 effector cytokines, including IL-4, IL-5, and IL-13. *[Adapted from M. L. Kapsenberg, 2003, Dendritic-cell control of pathogen-driven T-cell polarization,* Nature Reviews Immunology *3:984.]*

The Major Histocompatibility Complex Coordinates Interactions Among Immune Cells

also referred to as **human leukocyte antigens** (HLAs) because they were first identified on leukocytes and are expressed in high concentrations on lymphocytes. HLAs orchestrate many of the cell– cell interactions fundamental to immune responses. As described above, productive interactions between cells of the immune system require histocompatibility. Conversely, these antigens are major immunogens and thus targets in transplant rejection. The MHC includes class I, II and III antigens.

Class I MHC Molecules

Class I histocompatibility antigens are heterodimeric structures consisting of two chains and nonpolymorphic molecule called 2-microglobulin. The latter is a superficial surface protein lacking a membrane component and is noncovalently associated with the larger heavy chain. These antigens are recognized by cytotoxic T cells during graft rejection or T-lymphocyte–mediated killing of virus-infected cells.

Class II MHC Molecules

Class II molecules are heterodimers that consist of two noncovalently linked glycoprotein chains Both chains are transmembrane proteins.

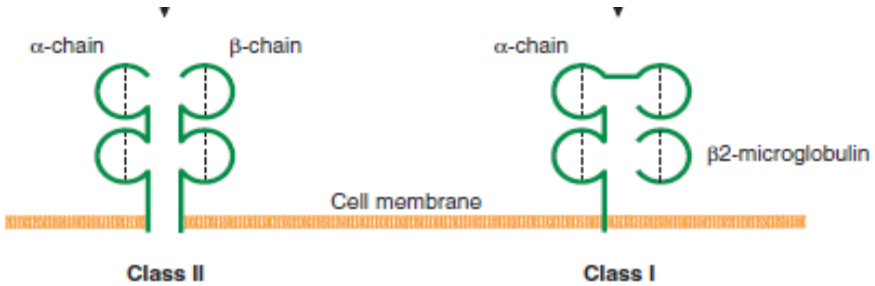


FIGURE 4-7. The highly polymorphic loci that encode major histocompatibility antigens are located on the short arm of chromosome 6. Class I and class II molecules exhibit different structures, but each participates in fundamentally important cell–cell interactions. Class III genes encode some complement components that are not formally histocompatibility antigens.

T-Lymphocyte Interactions:-

T lymphocytes recognize specific antigens, usually proteins or haptens bound to proteins. They undergo a series of activation events when engaged via the TCR in the context of histocompatible (i.e., MHC-matched) APC.

B-Lymphocyte Interactions:-

The initial stimulus leads to B-cell proliferation and clonal expansion, a process amplified by cytokines from both accessory cells and T cells. If no additional signal is provided, proliferating B cells return to a resting state and enter the memory cell pool.

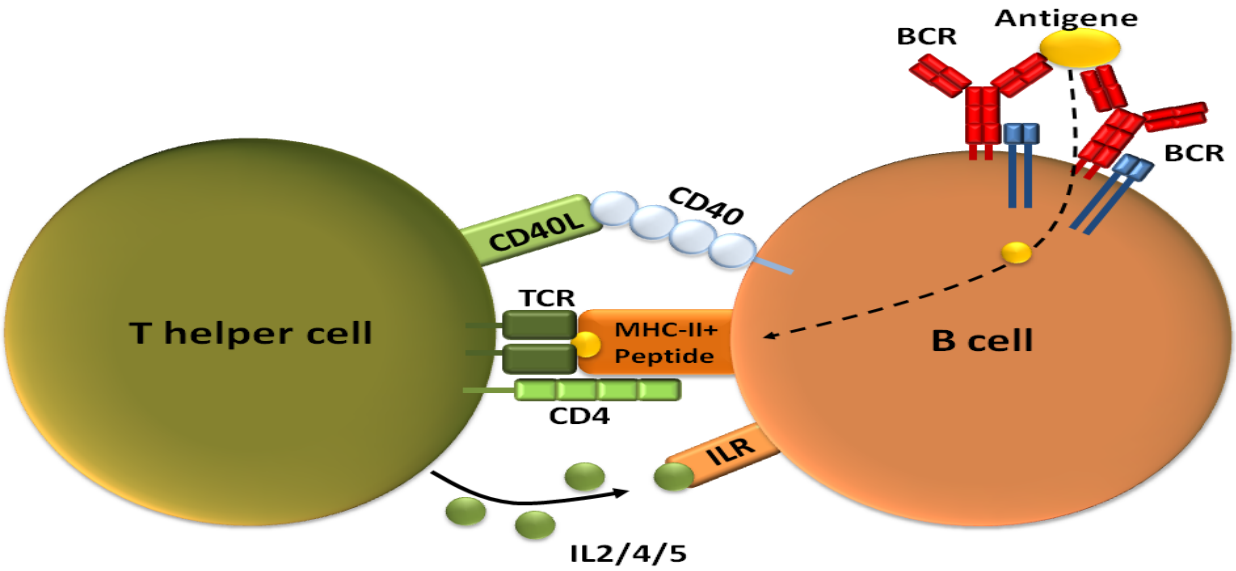
Mononuclear Phagocyte Activities

Mononuclear phagocyte is a general term applied to phagocytic cell populations in virtually all organs and connective tissues. Among these cells are macrophages, monocytes, Kupffer cells of the liver and lung alveolar macrophages. The older term “histiocyte” is synonymous with **macrophage** either a circulating or a fixed tissue macrophage. This system, formerly known as the “reticuloendothelial system,” is now termed the **mononuclear phagocyte**

system. In addition to their "housekeeping" functions, macrophages are critical in inducing immune responses and in maintenance and resolution of inflammatory reactions.

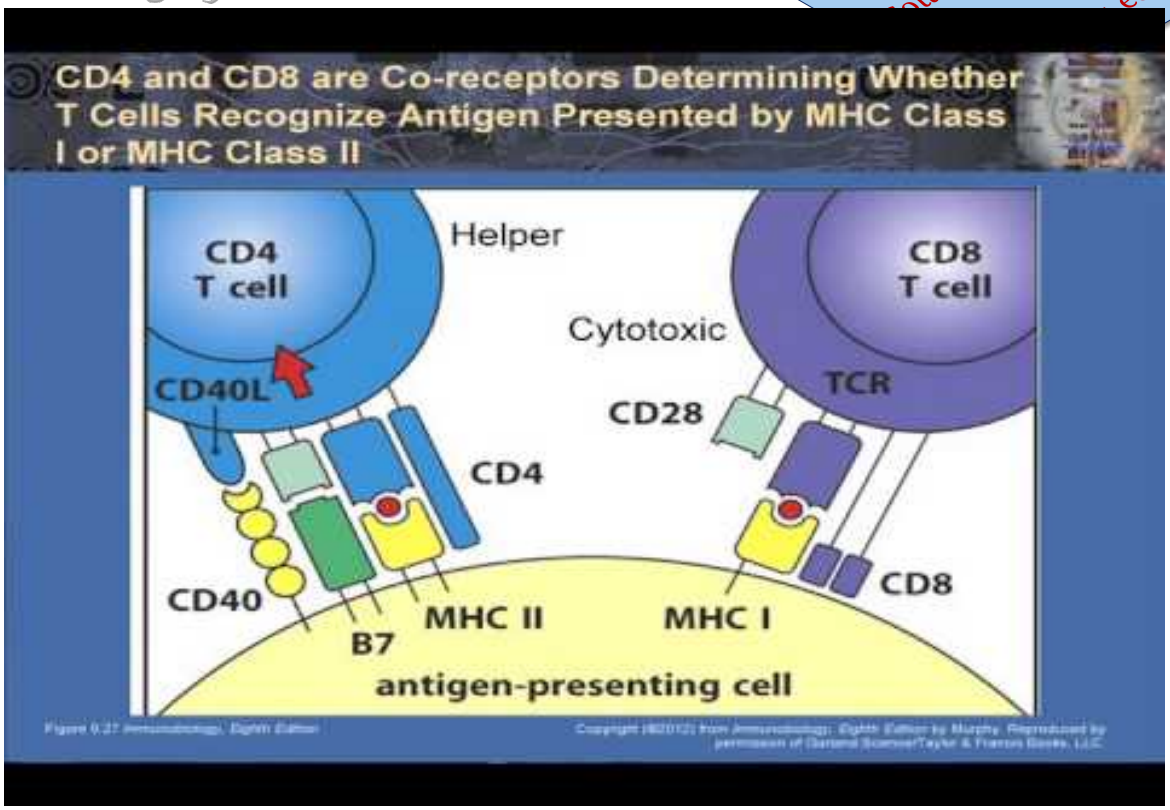
B-cell activation:-

B cell activation begins when the B cell binds to an antigen via its BCR, Antigen is presented to lymphocytes by APCs such as macrophages or dendritic cells (DCs) When a BCR binds an antigen tagged with a fragment of the C3 complement protein, CD21 binds the C3 fragment, co-ligates with the bound BCR, and signals are transduced through CD19 and CD81 to lower the activation threshold of the cell



T-cell activation:

T lymphocytes recognize specific antigens, usually proteins or haptens bound to proteins. They undergo a series of activation events when engaged via the TCR in the context of histocompatible (i.e., MHC-matched) APC.



Clinical Evaluation of Immune Status

1-Total Immunoglobulin Concentration Is Determined by Electrophoresis

2- Antibody-Dependent Immunity Can Be Assessed by Testing for Antibodies Against Specific Antigens

3- Cell-Mediated Immunity Can Be Assessed Using Peripheral Blood T Cells or Skin Sensitivity Testing

4- Lymphocyte Populations Are Quantitated by Flow Cytometry

5- Molecular Evaluation of Immune Status Facilitates Diagnosis of Rare Immune System Defects

Immunologically Mediated Tissue Injury:-

Immune responses not only protect against invasion by foreign organisms but may also cause tissue damage. the protective effects of an immune response give way to deleterious effects associated with a spectrum of lesions Immune- or hypersensitivitymediated diseases

are common and include such entities as hives (urticaria), asthma, hay fever, hepatitis, glomerulonephritis and arthritis. Hypersensitivity reactions are classified according to the type of immune mechanism. Type I, II and III hypersensitivity reactions all require formation of a specific antibody to an exogenous (foreign) or an endogenous (self) antigen.

Type I, II and III hypersensitivity reactions all require formation of a specific antibody to an exogenous (foreign) or an endogenous (self) antigen

1-**type I, or immediate-type hypersensitivity**, reactions, IgE antibody Type I or Immediate Hypersensitivity Reactions Are Triggered by IgE Bound to Mast Cells, *Immediate-type hypersensitivity is manifested by a localized or generalized reaction that occurs immediately (within minutes) after exposure to an antigen or "allergen" to which the person has previously been sensitized*.

(CD4_, Th2 T-cell–dependent mechanism and that bind avidly to Fc-epsilon (Fc) receptors on mast cells and basophils.)

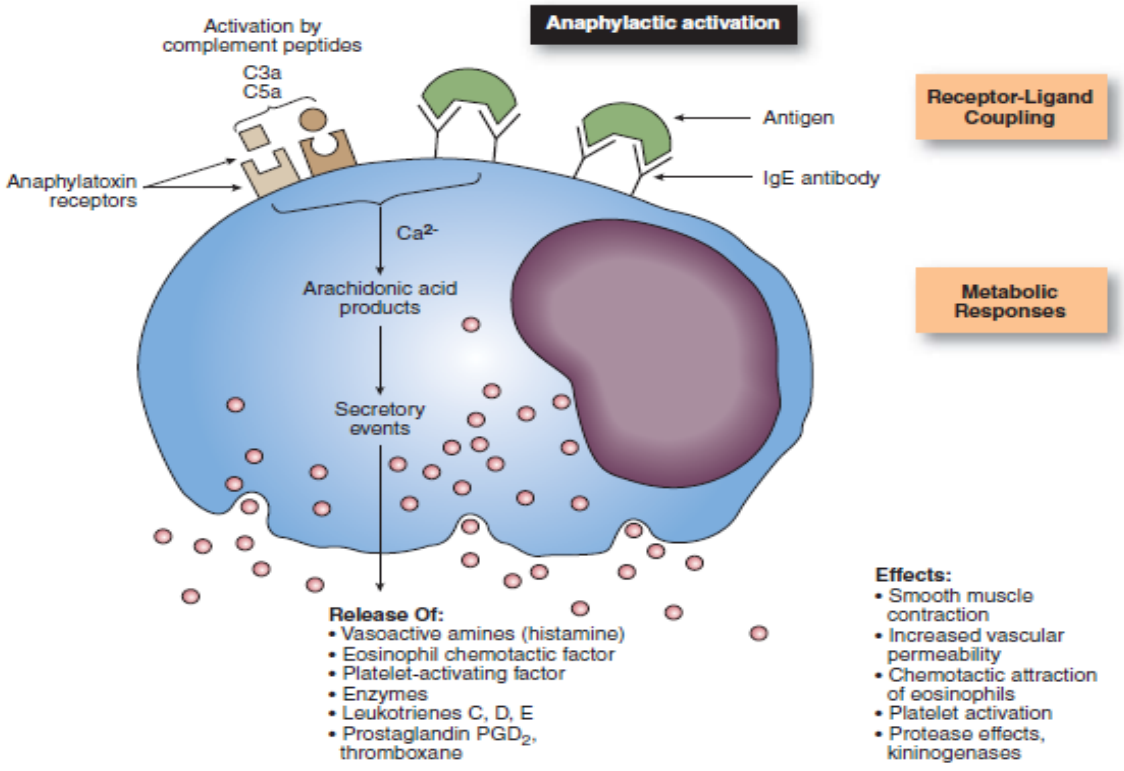
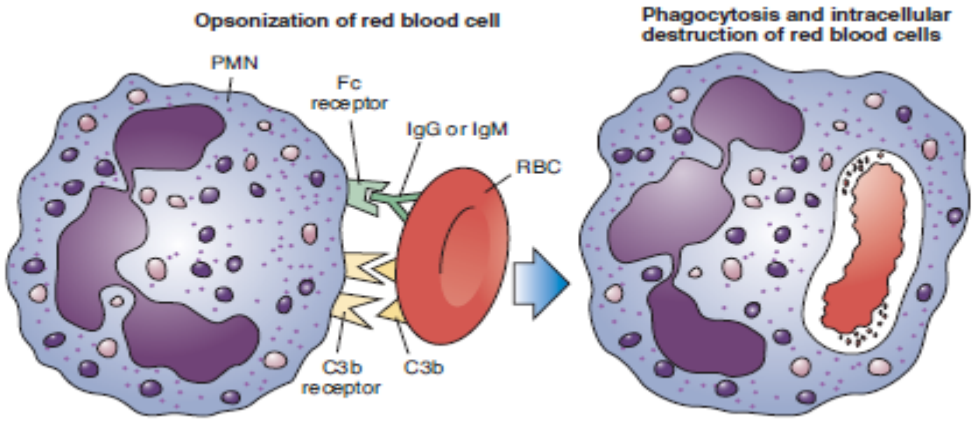


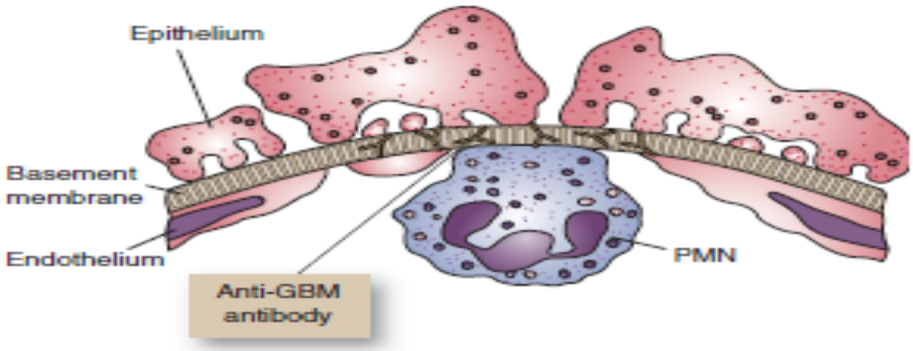
FIGURE 4-9. In a type I hypersensitivity reaction, allergen binds to cytophilic surface IgE antibody on a mast cell or basophil and triggers cell activation and the release of a cascade of proinflammatory mediators. These mediators are responsible for smooth muscle contraction, edema formation and the recruitment of eosinophils. Ca^{2+} = calcium ion; Ig = immunoglobulin; PGD_2 = prostaglandin D_2.

2-type II hypersensitivity reactions, IgG or IgM antibody is formed against an antigen, usually a protein on a cell surface. Less commonly, the antigen is an intrinsic structural component of the extracellular matrix (e.g., part of the basement membrane). Such antigen–antibody coupling activates complement,

Type II Hypersensitivity Reactions Are Mediated by Antibodies Against Fixed Cellular or Extracellular Antigens *IgG and IgM typically mediate type II reactions. An important characteristic of these antibodies is their ability to activate complement through the immunoglobulin Fc domain.* There are several antibody-dependent mechanisms of tissue injury.

(IgM or IgG antibody binds an antigen at the erythrocyte membrane. At sufficient density, the bound immunoglobulin fixes complement via C1q and the classical pathway (see Chapter 2). Activated complement can destroy target cells by several mechanisms. Complement products can lyse target cells directly, via C5b-9 complement complexes (Fig. 4-10). This complex, called the membrane attack complex)





3-type III hypersensitivity reactions, the antibody responsible for tissue injury is also usually IgM or IgG, but the mechanism of tissue injury differs. The antigen circulates in the vascular compartment until it is bound by antibody. The resulting immune complex is deposited in tissue. In Type III Hypersensitivity Reactions Immune Complex Deposition or Formation in Situ Leads to Complement Fixation and Inflammation *IgG, IgM and occasionally IgA antibody against a circulating antigen or an antigen that is deposited or "planted" in a tissue can cause a type III response.*

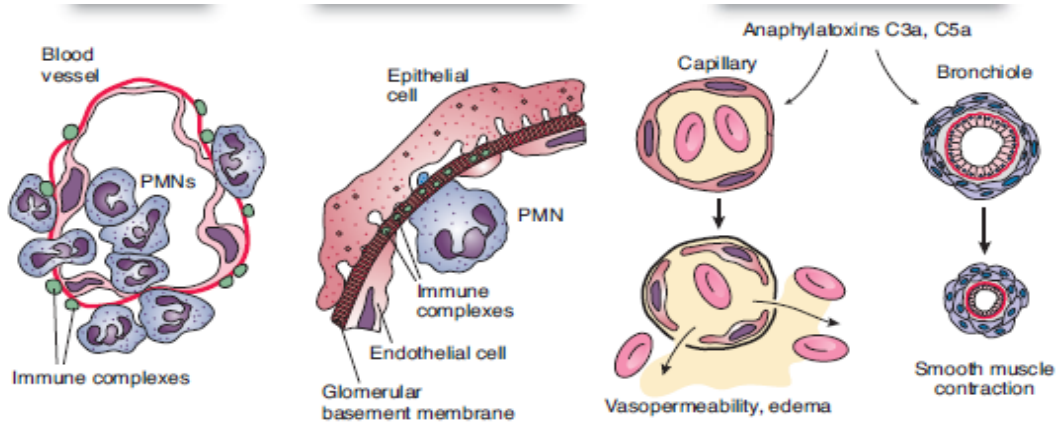
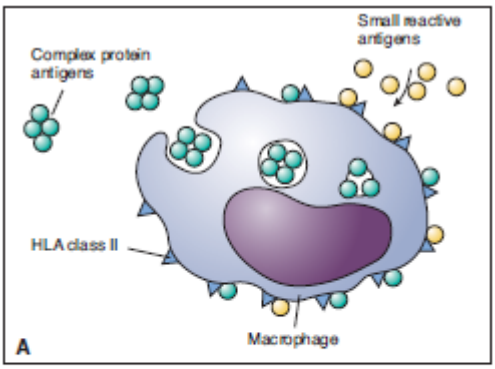
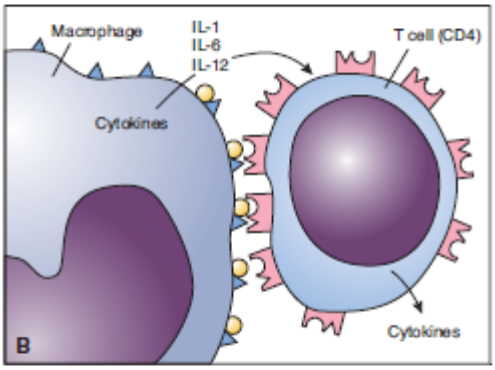
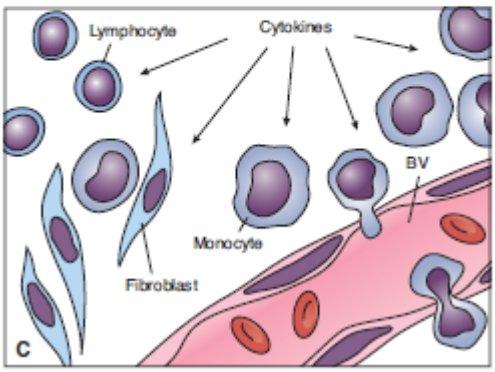


FIGURE 4-14. In type III hypersensitivity, immune complexes are deposited and can lead to complement activation and the recruitment of tissue-damaging inflammatory cells. The ability of immune complexes to mediate tissue injury depends on size, solubility, net charge and ability to fix complement. PMN = polymorphonuclear neutrophil.

4-Type IV reactions, or cell-mediated or delayed-type, hypersensitivity reactions, do not involve antibodies. Rather, antigen activation of T lymphocytes, usually with the help of macrophages, Type IV, or Cell-Mediated, Hypersensitivity Reactions Are Cellular Immune Responses *Classically, delayed-type hypersensitivity is a tissue reaction, mainly involving lymphocytes and mononuclear phagocytes, occurring in response to a soluble protein antigen and reaching peak intensity 24 to 48 hours after initiation.*







Modified Gell and Coombs Classification of Hypersensitivity Reactions

Type	Mechanism	Examples
Type I (anaphylactic type): immediate hypersensitivity	IgE antibody-mediated mast cell activation and degranulation	Hay fever, asthma, hives, anaphylaxis
	Non–IgE mediated	Physical urticarias
Type II (cytotoxic type): cytotoxic antibodies	Cytotoxic (IgG, IgM) antibodies formed against cell surface antigens; complement usually involved	Autoimmune hemolytic anemias, Goodpasture disease
	Noncytotoxic antibodies against cell surface receptors	Graves disease
Type III (immune complex type): immune complex disease	Antibodies (IgG, IgM, IgA) formed against exogenous or endogenous antigens; complement and leukocytes (neutrophils, macrophages) often involved	Autoimmune diseases (SLE, rheumatoid arthritis), many types of glomerulonephritis
Type IV (cell-mediated type): delayed-type hypersensitivity	Mononuclear cells (T lymphocytes, macrophages) with interleukin and lymphokine production	Granulomatous disease (tuberculosis)
		Delayed skin reactions (poison ivy)

Immunodeficiency Diseases:-

1-Primary Antibody Deficiency Diseases Are Characterized by Impaired Production of Antibodies:-

Bruton X-Linked Agammaglobulinemia

Bruton X-linked agammaglobulinemia (XLA) typically presents in male infants at 7 to 9 months old, at which time maternal antibody levels have declined.

Selective IgA Deficiency

Selective IgA deficiency is the most common primary immunodeficiency syndrome. It is characterized by normal serum levels of IgG and IgM and low serum (_7 mg/dL) and secretory concentrations of IgA.

Common Variable Immunodeficiency

CVID is a heterogenous group of disorders characterized by severe hypogammaglobulinemia and attendant infections apparently due to a variety of defects in Blymphocyte maturation or T-cell–mediated B-lymphocyte maturation.

Transient Hypogammaglobulinemia of Infancy

Prolonged hypogammaglobulinemia occurs in transient hypogammaglobulinemia of infancy after maternal antibodies in the infant have reached their nadir

Hyper-IgM Syndrome

This syndrome is often classified as a humoral immunodeficiency because immunoglobulin production is disordered. Patients have subnormal IgG, IgA and IgE levels and elevated IgM concentrations.

2-Primary T-Cell Immunodeficiency Diseases Typically Result in Recurrent or Protracted Viral and Fungal Infections:

DiGeorge Syndrome:

The syndrome is caused by defective development of the third and fourth pharyngeal pouches, which give rise to the thymus and parathyroid glands and influence conotruncal cardiac development.

Chronic Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis is the result of a congenital defect in T-cell function. It is characterized by susceptibility to candidal infections and is associated with an endocrinopathy (hypoparathyroidism, Addison disease, diabetes mellitus). Although most T-cell functions are intact, there is an impaired response to Candida antigens.

3-Combined Immunodeficiency Diseases Exhibit Reduced Immunoglobulins and Defects in T-Lymphocyte Function

Severe Combined Immunodeficiency:

Severe combined immunodeficiency (SCID) encompasses a large and heterogeneous group of disorders associated by deficiencies in T-cell and B-cell development and function. Affected patients present in the first few months of life with recurrent, often severe infections, diarrhea and failure to thrive. Some forms of SCID are also marked by nonimmunologic developmental defects.

***Autoimmunity and Autoimmune Diseases:-**

1-Immune Responses Against Self-Antigens:

Autoimmunity implies that the immune system no longer effectively differentiates between self- and non–self-antigens.

-Inaccessible Self-Antigens.

-Abnormal T-Cell Function.

-Molecular Mimicry.

-Polyclonal B-Cell Activation.

-Tissue Injury in Autoimmune Diseases.