The MHC Locus Encodes Three Major Classes of Molecules

The major histocompatibility complex is a collection of genes arrayed within a long continuous stretch of DNA on chromosome 6 in humans and on chromosome 17 in mice.

The MHC is referred to as the **human leukocyte antigen (HLA) complex** in humans and as the **H-2 complex** in mice, the two species in which these regions have been most studied.

Although the arrangement of genes is somewhat different in the two species, in both cases the MHC genes are organized into regions encoding three classes of molecules (Figure 8-7):

- **Class I MHC genes** encode glycoproteins expressed on the surface of nearly all nucleated cells; the major function of the class I gene products is presentation of endogenous peptide antigens to CD8_ T cells.
- **Class II MHC genes** encode glycoproteins expressed predominantly on APCs (macrophages, dendritic cells, and B cells), where they primarily present exogenous antigenic peptides to CD4_ T cells.
- **Class III MHC genes** encode several different proteins, some with immune functions, including components of the complement system and molecules involved in inflammation.

NINTH LECTURE

- The second signal is provided by an activated T cell, which binds to the B cell both through its antigen receptor and via a separate interaction between CD40 on the B cell and CD40L (CD154) on the activated TH cell. The bound T cell then delivers cytokines(IL-2&IL-4) and other signals to its partner B cell to complete the activation process.
- The second type of response, which directed toward multivalent or highly polymerized antigens, and does not require T-cell help. This type of response is referred to as a T-independent response, and the antigens that elicit such responses are T-independent (TI) antigens. One class of TI antigens (TI-1 antigens), exemplified by the lipopolysaccharide moiety of Gram-negative bacteria، interacts with the B cell via both mIg and innate immune receptors.

Humoral immune response

mature B cells, located in the peripheral lymphoid organs, encounter antigen. The two major types of B-cell responses are elicited by structurally distinct types of antigens.

- The first type of response that we will describe is generated upon recognition of protein antigens and requires the participation of CD4 helper T cells. Because T cells are involved, this class of B-cell response is therefore known as a T-dependent (TD) response, and it is mediated by B-2 B cells binding to TD antigens.
- Because B-2 B cells represent the majority of B cells, we will routinely refer to the B-2 B-cell subset simply as “B cells,” and distinguish the other B-cell subclasses by their particular names as B-1, marginal zone, or B-10 B cells.
- The T-dependent response requires two distinct signals. The first is generated when a multivalent antigen binds and cross-links membrane immunoglobulin receptors (mIg)

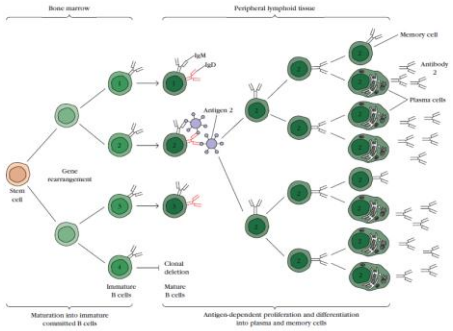
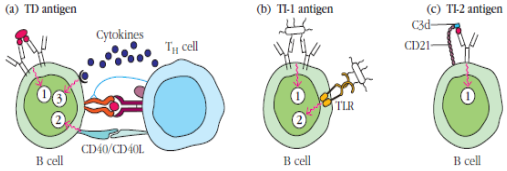


FIGURE 12-2 Maturation and clonal selection of B lymphocytes. B-cell maturation, which occurs in the absence of antigen, first produces immature B cells bearing IgM receptors. Each B cell bears receptors of one specificity only. Any B cell with receptors specific for antigens expressed in the bone marrow are deleted at the immature B cells stage (indicated by clone 4). Those B cells that do not express self-reactive receptors mature to express both IgM and IgD receptors and are released into the periphery, where they recirculate among the blood, lymph, and lymphoid organs. Clonal selection occurs when an antigen binds to a B cell with a receptor specific for that antigen. Clonal expansion of an antigen-activated B cell (number 2 in this example) leads to a clone of effector B cells and memory B cells; all cells in the expanded clone are specific for the original antigen. The effector, plasma cells secrete antibody reactive with the activating antigen.

TI-1 antigens are mitogenic (induce proliferation) for most B cells at high concentrations, as a result of their ability to bind to pattern recognition receptors (PRRs) on the surface of the B cell. However, at lower concentrations they activate only those B cells that bind antigen with their Ig receptors . The other class of TI antigens, TI-2 antigens, includes highly repetitive antigens, such as bacterial capsular polysaccharides.



opsonization

refers to the ability of antibodies to promote and/or enhance the engulfment of antigens by phagocytes.
In the case of opsonization, binding of pathogen (antigen)-antibody complexes to an Fc receptor on phagocytes will induce internalization of the complex and internal digestion of the pathogen in lysosomes .

Complement Fixation

antigen-antibody complexes also induce a complement cascade. Specifically, when antibodies that associate with complement bind to the surface of bacteria and some (enveloped) viruses, they can initiate a cascade of reactions that results in the generation of the membrane attack complex (MAC), perforating pathogen membranes and killing the microbe.

Antibody-dependent cell-mediated cytotoxicity (ADCC)

Antibody-antigen complexes are bound by Fc receptors on NK cells and granulocytes, thus directing the cytotoxicity of these cells toward the antigen targeted by the antibody

Antibody-Mediated Effector Functions

1-Neutralization

blocking pathogen entry into cells (neutralization) and they can prevent a pathogen from ever initiating an infection. They are referred to as neutralizing antibodies.Pathogens disarmed by neutralizing antibodies are typically phagocytosed by macrophages.Neutralizing antibodies can also block entry of toxins into cells

T - helper cells can be further subdivided into Th 1, Th 2 and Th 17 cells on the basis of the cytokine profiles that these cells secrete , as this confers different effector functions on such cells.

Cytokines act as intercellular messengers

- Cytokines are structurally diverse polypeptides that function as messenger molecules that can communicate signals from one cell type to another and, amongst other things, can instruct the cell receiving the signal to proliferate, differentiate, secrete additional cytokines, migrate or die. To date, many different cytokines have been described and no doubt some remain to be discovered .

CELL–MEDIATED IMMUNE RESPONSE

Host defense in which T lymphocytes serve as effector cells is called **cell-mediated immunity.** T cells are essential for eliminating microbes that survive and replicate inside cells. Cell-mediated immune responses begin with the activation of naive T cells to proliferate and to differentiate into effector cells. These effector T cells eliminate cell-associated microbes, often working together with macrophages and other leukocytes.

TYPES OF T CELL–MEDIATED IMMUNE REACTIONS

- **Two types of cell-mediated immune reactions are designed to eliminate different types of microbes.**
- **CD4+ helper T cell secrete cytokines that recruit and activate other leukocytes to phagocytose (ingest) and destroy microbes.**
- **CD8+ cytotoxic T lymphocytes (CTLs) kill any infected cell containing microbial proteins in the cytosol or nucleus, eliminating cellular reservoirs of infection**

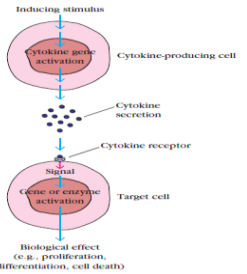


FIGURE 4-2 Overview of the induction and function of cytokines. An inducing stimulus, which may be an antigen or another cytokine, interacts with a receptor on one cell, inducing it to secrete cytokines that in turn act on receptors of a second cell, bringing about a biological consequence. In the case of IL-2, both cells may be antigen-activated T cells that secrete IL-2, which acts both on the secreting cell and on neighboring, activated T cells.

- One of the most important cytokine groupings, to the immunologist ' s way of thinking, is the interleukin family as this contains cytokines that act as communicators between leukocytes.

- The interaction of a cytokine with its receptor on a target cell can cause changes in the expression of adhesion molecules and chemokine receptors on the target membrane, thus allowing it to move from one location to another. Cytokines can also signal an immune cell to increase or decrease the activity of particular enzymes or to change its transcriptional program, thereby altering and enhancing its effector functions.

- Cytokines that act on cells some distance away from the secreting cell, such that they must pass through the bloodstream before reaching their target, are referred to as **endocrine** (Figure 4-1).
- Those that act on cells near the secreting cell, such that the cytokine merely has to diffuse a few ingstroms through tissue fluids or across an immunological synapse, are referred to as **paracrine**.
- Sometimes, a cell needs to receive a signal through its own membrane receptors from a cytokine that it, itself, has secreted. This type of signaling is referred to as **autocrine**.

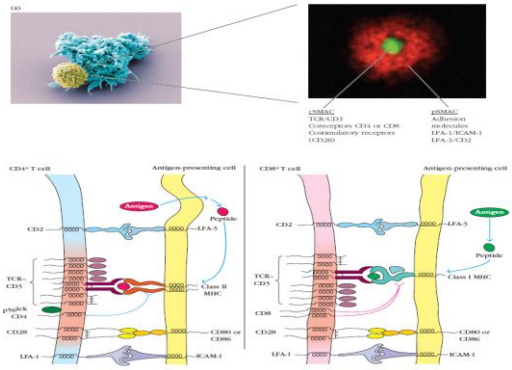
- Approximately 34 interleukins have been described to date (IL - 1 to IL - 35) with the status of IL - 14 as an interleukin in doubt.
- Other cytokine families have been established on the basis of their ability to support proliferation of hematopoietic precursors (colony stimulating factors), or cytotoxic activity towards transformed cell types (tumor necrosis factors), or the ability to interfere with viral replication (interferons).
- Although the term *cytokine* refers to all molecules that communicate among immune cells, the name **chemokine** is used specifically to describe that subpopulation of cytokines that share the specific purpose of mobilizing immune cells from one organ, or indeed, from one part of an organ, to another. Chemokines belong to the class of molecules called **chemoattractants**, molecules that attract cells by influencing the assembly, disassembly, and contractility of cytoskeleton proteins and the expression of cell-surface adhesion molecules.
- Chemokines attract cells with the appropriate chemokine receptors to regions where the chemokine concentration is highest.

TABLE 4-2 Six Cytokine Families

Family name	Representative members of family	Comments
Interleukin 1 family	IL-1α, IL-1β, IL-1Ra, IL-18, IL-33	IL-1 was the first noninterferon cytokine to be identified. Members of this family include important inflammatory mediators.
Hematopoietin (Class I cytokine) family	IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-12, IL-13, IL15, IL-21, IL-23, GM–CSF, G-CSF, Growth hormone, Prolactin, Erythropoietin/hematopoietin	This large family of small cytokine molecules exhibits striking sequence and functional diversity.
Interferon (Class II cytokine) family	IFN-α, IFN-β, IFN-γ, IL-10, IL-19, IL-20, IL-22, IL-24	While the IFNs have important roles in anti-viral responses, all are important modulators of immune responses.
Tumor Necrosis Factor family	TNF-α, TNF-β, CD40L, Fas (CD95), BAFF, APRIL, LTβ	Members of this family may be either soluble or membrane bound; they are involved in immune system development, effector functions, and homeostasis.
Interleukin 17 family	IL-17 (IL17-A), IL17B, C, D, and F	This is the most recently discovered family; members function to promote neutrophil accumulation and activation, and are proinflammatory.
Chemokines (see Appendix III)	IL-8, CCL19, CCL21, RANTES, CCL2 (MCP-1), CCL3 (MIP-1α)	All serve chemoattractant function.

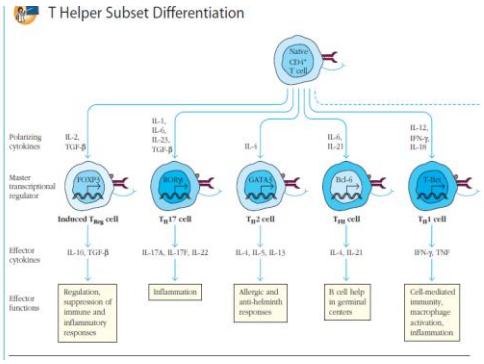
TABLE 4-1 Functional groups of selected cytokines*

Cytokine	Secreted by†	Targets and effects
SOME CYTOKINES OF INNATE IMMUNITY		
Interleukin 1 (IL-1)	Monocytes, macrophages, endothelial cells, epithelial cells	Vasculature (inflammation); hypothalamus (fever); liver (induction of acute phase proteins)
Tumor necrosis factor-α (TNF-α)	Macrophages, monocytes, neutrophils, activated T cells and NK cells	Vasculature (inflammation); liver (induction of acute phase proteins); loss of muscle, body fat (cachexia); induction of death in many cell types; neutrophil activation
Interleukin 12 (IL-12)	Macrophages, dendritic cells	NK cells; influences adaptive immunity (promotes T_H1 subset)
Interleukin 6 (IL-6)	Macrophages, endothelial cells, and T_H2 cells	Liver (induces acute phase proteins); influences adaptive immunity (proliferation and antibody secretion of B-cell lineage)
Interferon-α (IFN-α) (this is a family of molecules)	Macrophages dendritic cells, virus-infected cells	Induces an antiviral state in most nucleated cells; increases MHC Class I expression; activates NK cells
Interferon β (IFN-β)	Macrophages, dendritic cells, virus-infected cells	Induces an antiviral state in most nucleated cells; increases MHC Class I expression; activates NK cells
SOME CYTOKINES OF ADAPTIVE IMMUNITY		
Interleukin 2 (IL-2)	T cells	T-cell proliferation; can promote AICD. NK cell activation and proliferation; B-cell proliferation
Interleukin 4 (IL-4)	T_H2 cells, mast cells	Promotes T_H2 differentiation; isotype switch to IgE
Interleukin 5 (IL-5)	T_H2 cells	Eosinophil activation and generation
Transforming growth factor β (TGF-β)	T cells, macrophages, other cell types	Inhibits T-cell proliferation and effector functions; inhibits B-cell proliferation; promotes isotype switch to IgA; inhibits macrophages
Interferon γ (IFN-γ)	T_H1 cells, $CD8^+$ cells, NK cells	Activates macrophages; increases expression MHC Class I and Class II molecules; increases antigen presentation



T-Cell Activation and the Two-Signal Hypothesis

- not one but two signals were required for full T-cell activation: *Signal 1* is provided by antigen-specific TCR engagement (which can be enhanced by co receptors and adhesion molecules),
- and *Signal 2* is provided by contact with a costimulatory ligand, which can only be expressed by a functional APC. When a T cell receives both Signal 1 and Signal 2, it will be activated to produce cytokines that enhance entry into cell cycle and proliferation
- Interactions between adhesion molecules and their ligands (e.g., LFA-1/ICAM-1 and CD2/LFA-3) help to sustain the signals generated by allowing long-term cell interactions.
- Interactions between costimulatory receptors on T cells (e.g., CD28) and costimulatory ligands on dendritic cells (e.g., CD80/86) provide a second, required signal. In addition, as you will see below, a third set of signals, provided by local cytokines (Signal 3), directs T-cell differentiation into distinct effector cell types.



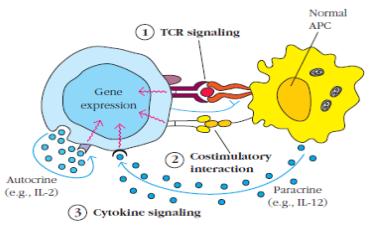


FIGURE 11-3 Three signals are required for activation of a naïve T cell. The TCR/MHC-peptide interaction, along with CD4 and CD8 coreceptors and adhesion molecules, provide Signal 1. Co-stimulation by a separate set of molecules, including CD28 (or ICOS, not shown) provide Signal 2. Together, Signal 1 and Signal 2 initiate a signal transduction cascade that results in activation of transcription factors and cytokines (Signal 3) that direct T-cell proliferation (IL-2) and differentiation (polarizing cytokines). Cytokines can act in an *autocrine* manner, by stimulating the same cells that produce them, or in a *paracrine* manner, by stimulating neighboring cells.