BP 605 T. Pharmaceutical Biotechnology (Theory)

Humoral immunity and Cellular immunity

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Overview

- Definition and Introduction
- Humoral Immunity and Cellular Immunity
- MHC Structure and Function

Specific Defense or Adaptive Immunity

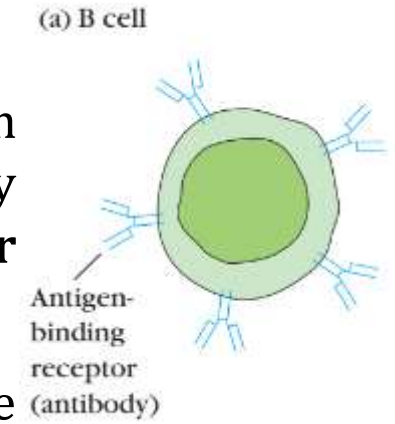
- ✓ A specific immune response is **provoked** when microbes **colonize.** Involves a **coordinated attack** by **B and T lymphocytes**
- ✓ Unlike innate immune responses, adaptive immune responses are not the same in all members of a species but are reactions to specific antigenic challenges.
- ✓ The adaptive immune system has four major characteristics:
- **Antigenic specificity;** B and T cells proliferate after activation
- **Diversity** of lymphocytes and receptors
- **Immunologic memory**
- **Self/nonself recognition;** lack of reactivity against an animal's own molecules
- ✓ Two major branches:

Humoral (Antibody-Mediated) = involves the production of antibodies by B cells (particularly good for microbes in body fluids)

Cellular (Cell-Mediated) = involves T cells directly attacking the microbe (particularly good for microbes hiding inside cells)

Humoral immune response

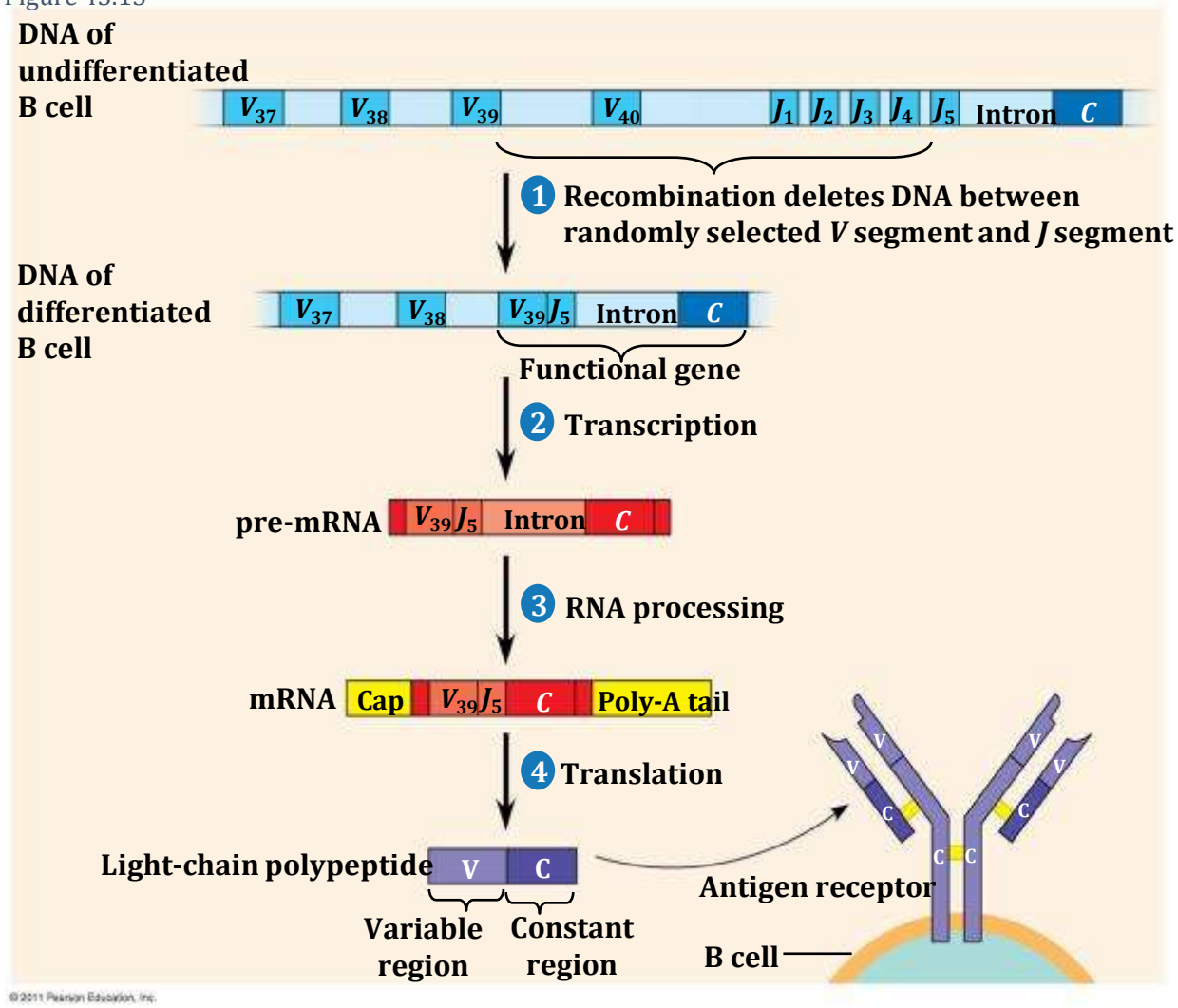
- ✓ **B lymphocytes** mature within the bone marrow; when they leave it, each expresses a unique antigen-binding receptor on its membrane.
- ✓ B-cell receptor is a **membrane-bound antibody molecule**. Antibodies are **glycoproteins** that consist of two **identical heavy polypeptide chains and two identical light polypeptide chains**.
- ✓ **Naive B cell** (one that has not previously encountered antigen) first encounters the antigen that matches its membrane bound antibody, the binding of the antigen to the antibody causes the cell to divide rapidly; its progeny differentiate into **memory B cells** and **effector B** cells called **plasma cells**.
- ✓ **Memory B cells have a longer life span than naive cells**, and they express the same membrane-bound antibody as their parent B cell.
- ✓ Plasma cells produce the antibody in a form that can be secreted and have **little or no membrane-bound antibody.** Plasma cells **live for only a few days and they secrete enormous amounts of antibody** (2000 molecules of antibody per second) during this time.
- ✓ **Secreted antibodies are the major effector molecules of humoral immunity**



Generation of B and T Cell Diversity

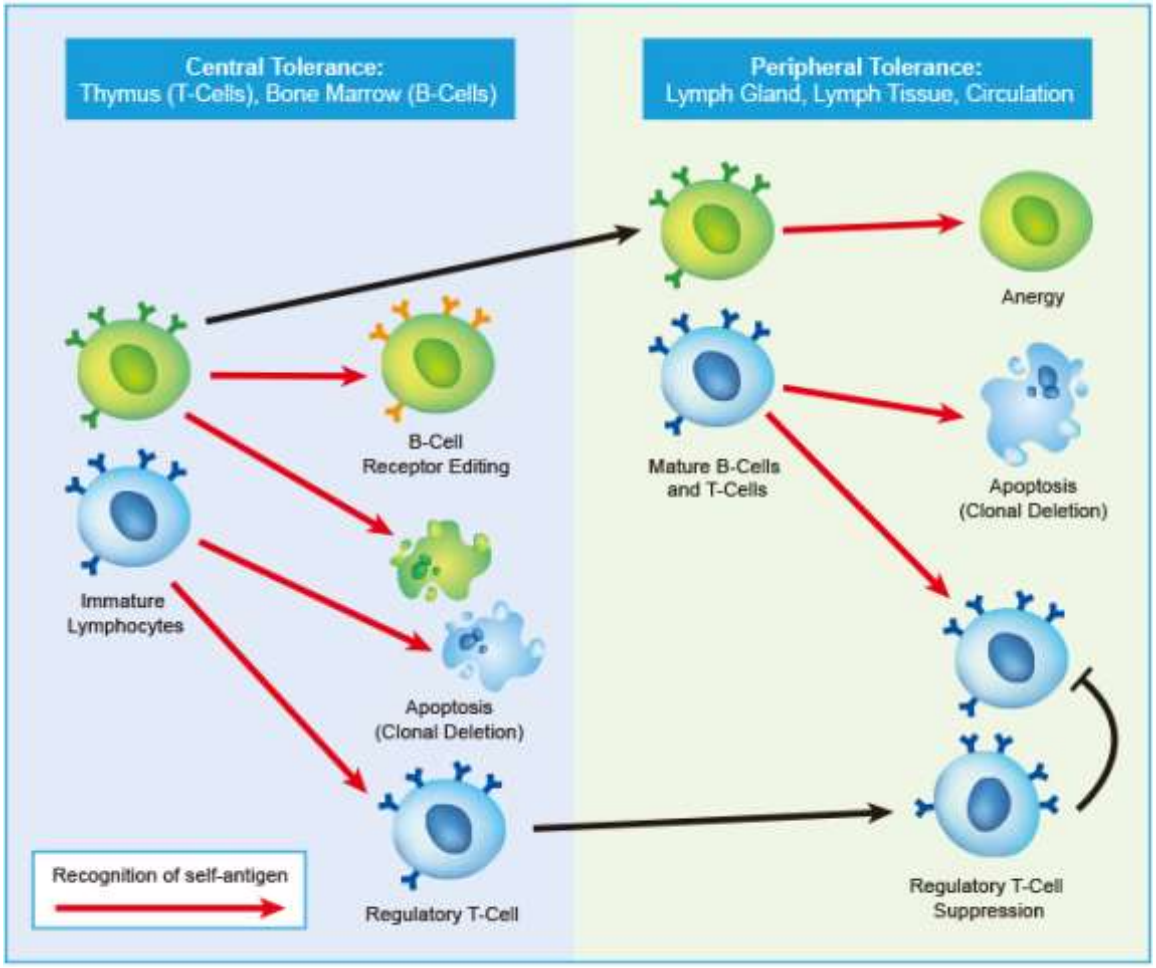
- ✓ By combining variable elements, the immune system assembles a diverse variety of antigen receptors
- ✓ The immunoglobulin (Ig) gene encodes one chain of the B cell receptor
- ✓ Many different chains can be produced from the same gene by rearrangement of the DNA
- ✓ Rearranged DNA is transcribed and translated and the antigen receptor formed.

Figure 43.13



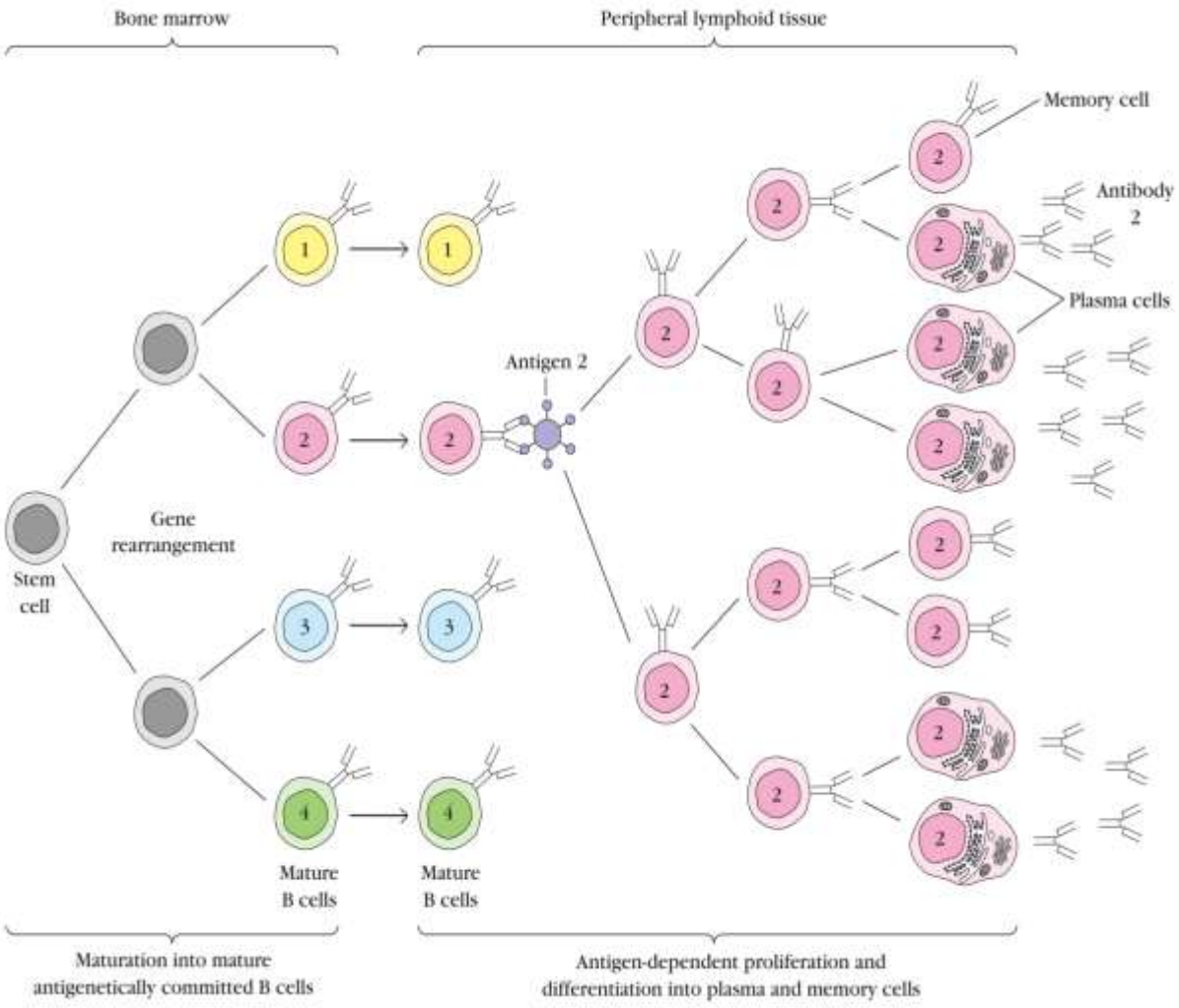
Origin of Self-Tolerance

- ✓ Antigen receptors are generated by random rearrangement of DNA
- ✓ As lymphocytes mature in bone marrow or the thymus, they are tested for self-reactivity
- ✓ Some B and T cells with receptors specific for the body's own molecules are destroyed by apoptosis, or programmed cell death
- ✓ The remainder are rendered nonfunctional



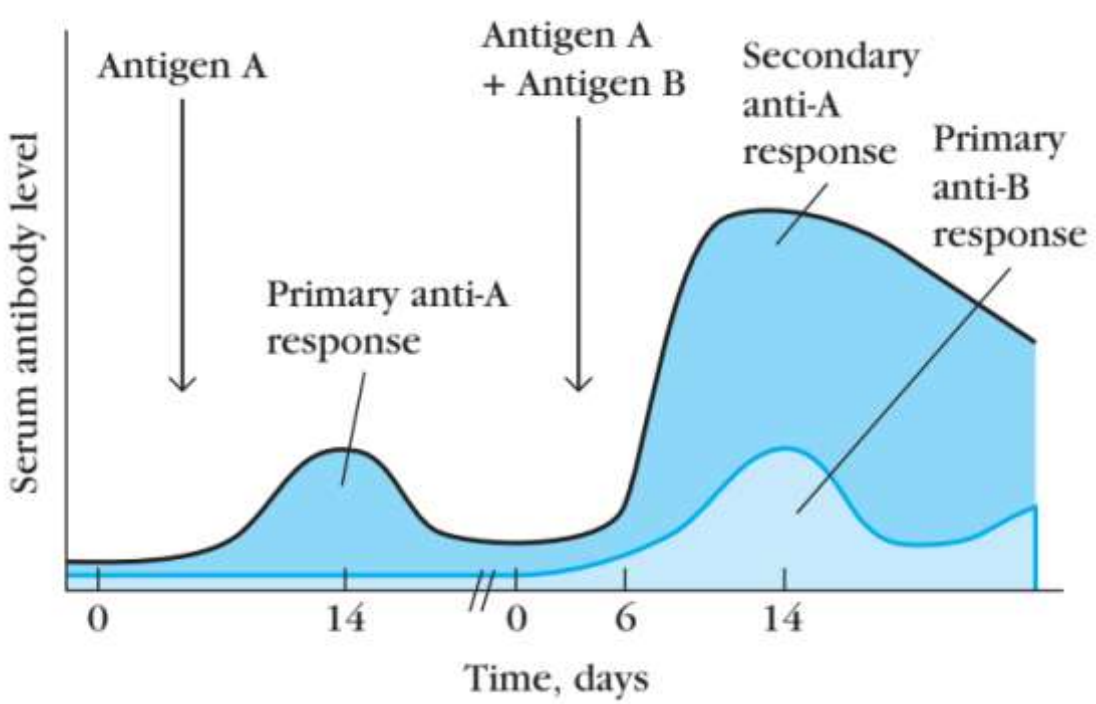
Proliferation of B Cells and T Cells

- ✓ **Clonal selection** occurs when an antigen binds to a B cell whose membrane bound antibody molecules are specific for epitopes on that antigen.
- ✓ **Clonal expansion** of an antigen-activated B cell leads to a clone of **memory B cells** and **effector B cells**, called **plasma cells**; all cells in the expanded clone are specific for the original antigen.
- ✓ The plasma cells secrete antibody reactive with the activating antigen.
- ✓ Similar processes take place in the T-lymphocyte population, resulting in clones of **memory T cells** and **effector T cells**; the latter include **activated T_H cells**, which secrete cytokines, and **cytotoxic T lymphocytes** (CTLs).



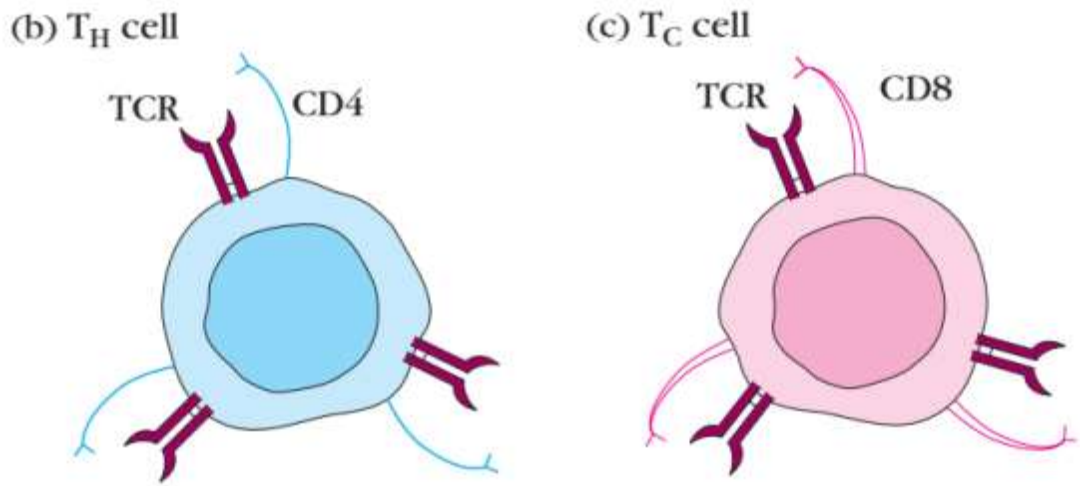
Immunological Memory

- ✓ Immunological memory is responsible for long-term protections against diseases, due to either a prior infection or vaccination
- ✓ The first exposure to a specific antigen represents the primary immune response
- ✓ During this time, selected B and T cells give rise to their effector forms
- ✓ In the secondary immune response, memory cells facilitate a faster, more efficient response.



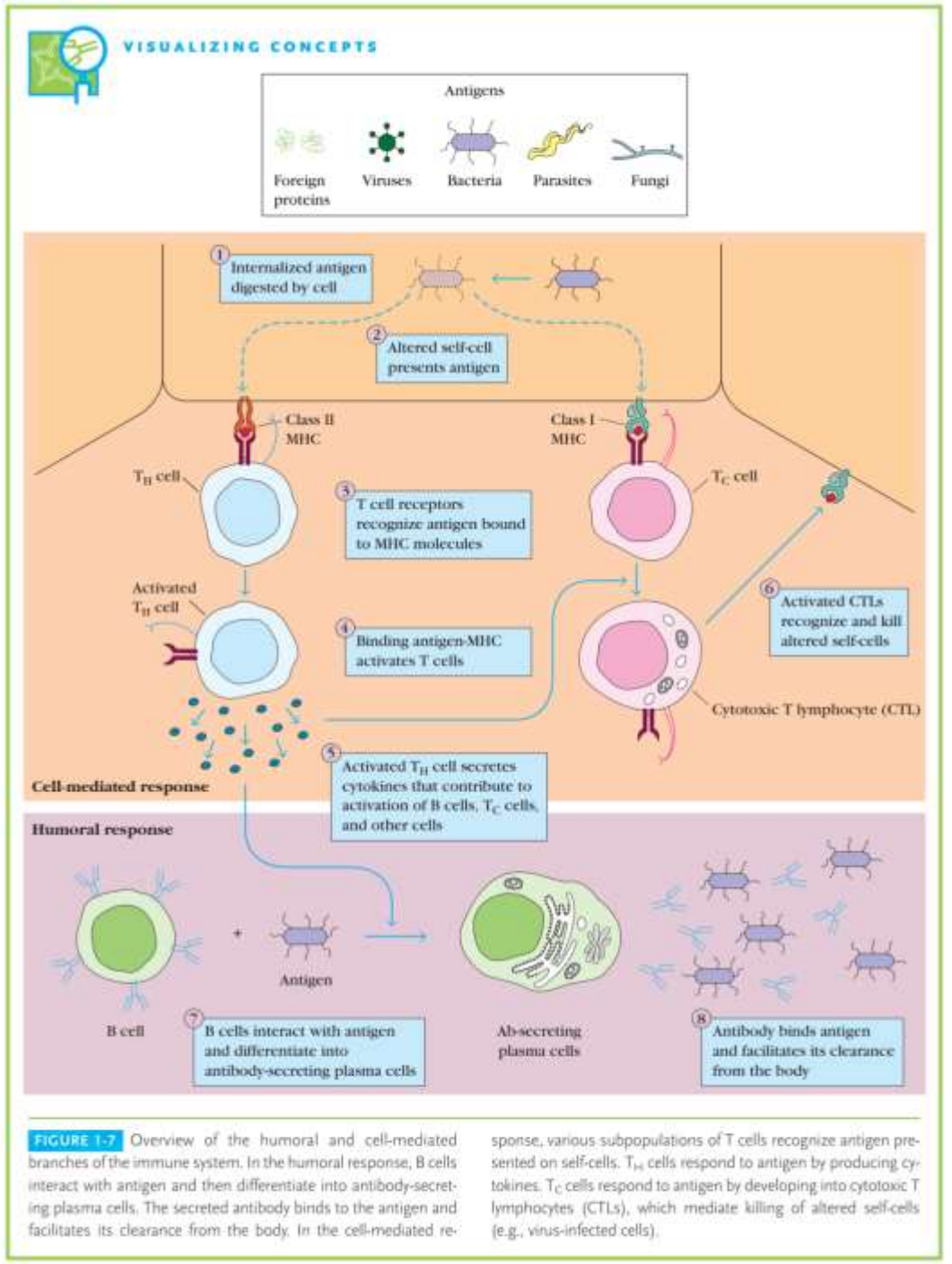
Cell-mediated immune response

- ✓ A type of T cell called a helper T cell triggers both the humoral and cell-mediated immune responses
- ✓ Signals from helper T cells initiate production of antibodies that neutralize pathogens and activate T cells that kill infected cells
- ✓ Antigen-presenting cells have class I and class II MHC molecules on their surfaces.



Cell-mediated....Contd...

- ✓ Class II MHC molecules are the basis upon which antigen-presenting cells are recognized.
- ✓ Antigen receptors on the surface of helper T cells bind to the antigen and the class II MHC molecule; then signals are exchanged between the two cells.
- ✓ The helper T cell is activated, proliferates, and forms a clone of helper T cells, which then activate the appropriate B cells.



Cell-Mediated.....contd....

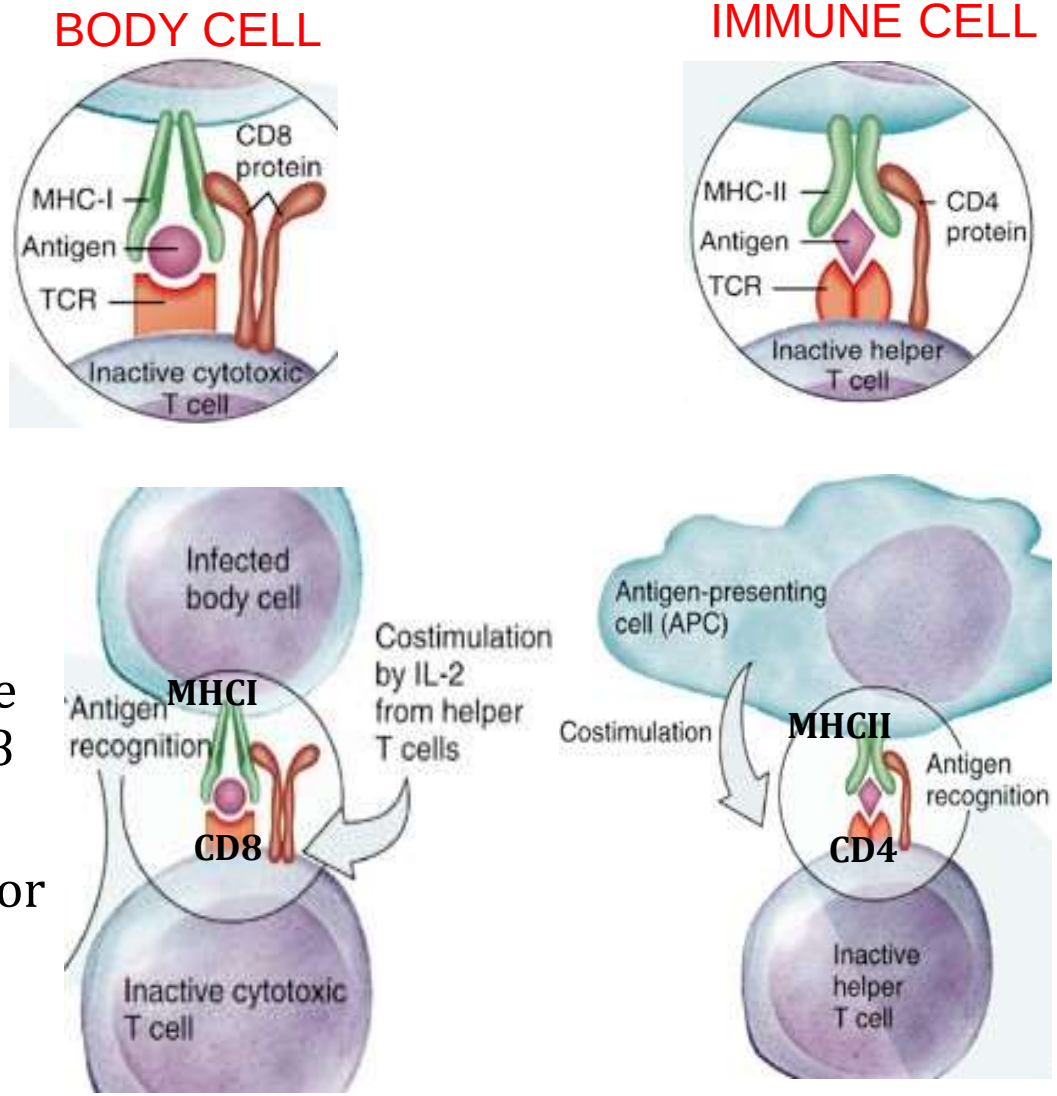
The immune response begins when the ***T*-cell** receptors (TCR) binds to the ***antigen (specificity)***

- **TCR/CD8** receptors on $\mathbf{T_C}$ bind to abnormal **MHC I** presenting antigen
- **TCR/CD4** receptors on $\mathbf{T_H}$ bind **MHC II** presenting antigen

Activation requires co-stimulation

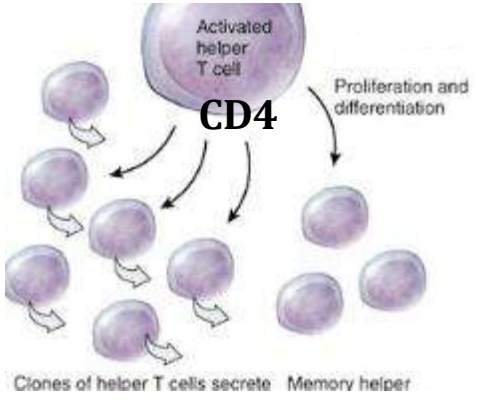
✓ After the initial binding B7 proteins (made when innate immune system is stimulated) on the APC bind to CD28 receptors on the T cells

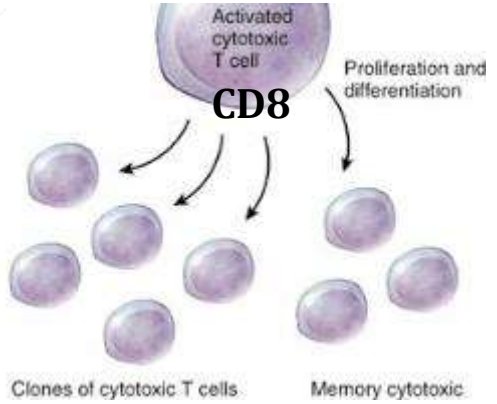
✓ After binding occurs chemical stimulation is required for the immune reaction to proceed

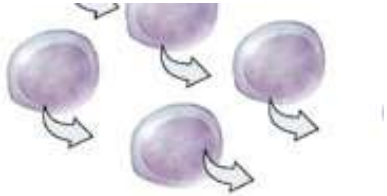


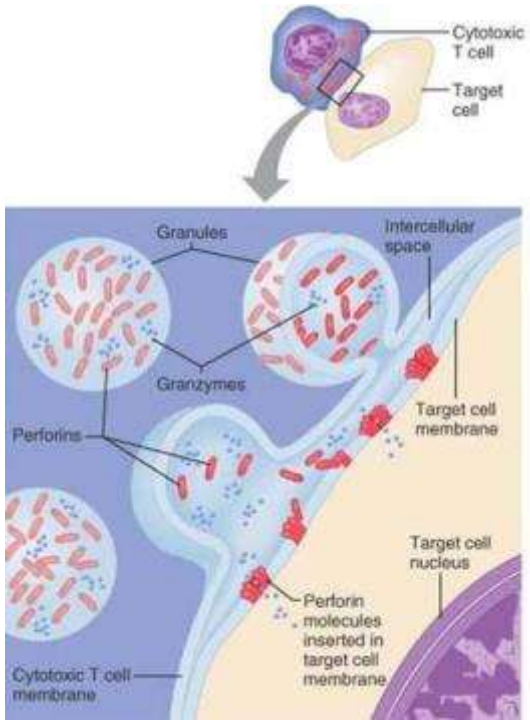
Cell-Mediated…..contd….

- ✓ Once activated by binding and costimulation, the T-lymphocyte rapidly divides to create an army of clones to fight the specific antigen
- ✓ Activated, Cloned Helper-T Cells (CD4) release chemicals that:
- Stimulate Cytotoxic T cells
- Stimulate B cells
- Enhance activity of macrophages and NK's
- ✓ Activated, **cloned Cytotoxic T- Lymphocytes directly attack microbe** with the specific antigen
- **Perforins** = make holes in membranes
- **Granzymes** = destroy proteins
- ✓ Memory T-Lymphocytes will attack the microbe more quickly next time it enter









Major Histocompatibility Complex (MHC)

"A linked cluster of genes encoding cell-surface molecules that play a role in intercellular recognition between self and non-self and are required for antigen presentation to T-cells."

Peter Goerer and Goerge Snell was awarded the **Nobel prize in 1980**.

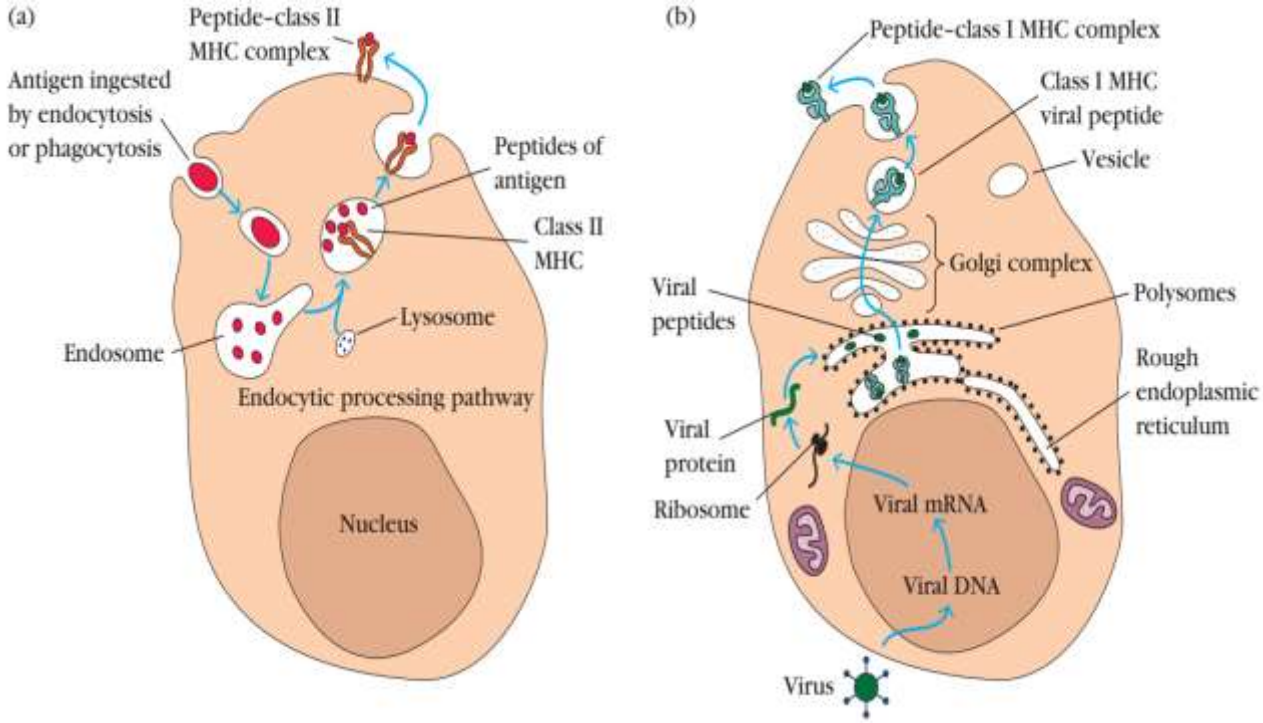
- ✓ Fundamentally important:
- basis of self / not self distinction
- presentation of processed antigen
- ✓ **MHC-I** are found on all body cells (**all nucleated cells**) except RBC's
- B & T cells do not respond to these proteins when they are "normal"
- Infected body cells/cancerous cells have abnormal MHC I proteins and will provoke a reaction
- ✓ **MHC II** are found on various immune cells (**B-cells, macrophages, dendritic cells**)
- Usually will include pieces of the microbe
- Used to present the antigen to other immune cells

MHC.....Contd...

Processing and presentation of exogenous and endogenous antigens.

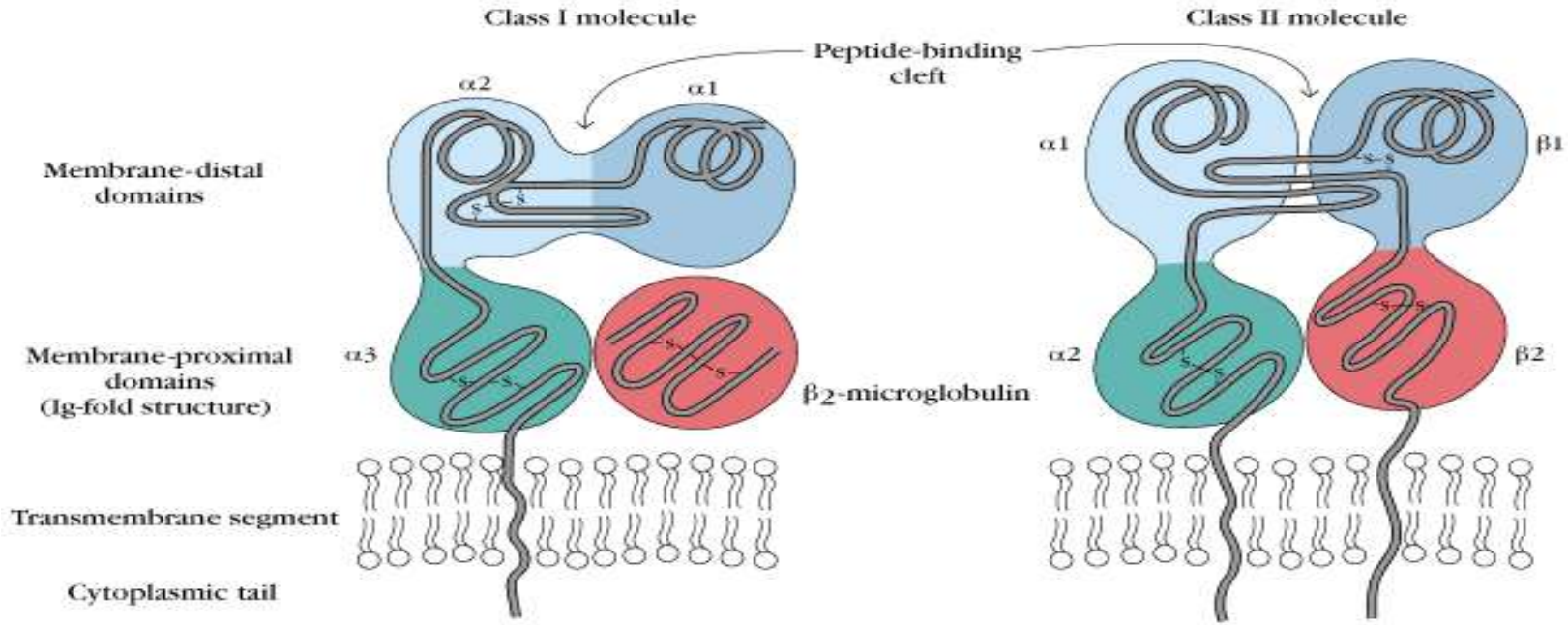
(a) **Exogenous antigen** is ingested by endocytosis or phagocytosis and then enters the endocytic processing pathway. Here, within an acidic environment, the antigen is degraded into small peptides, which then are presented with class II MHC molecules on the membrane of the antigen-presenting cell.

Endogenous antigen, which is produced within the cell itself (e.g., in a virus infected cell), is degraded within the cytoplasm into peptides, which move into the endoplasmic reticulum, where they bind to class I MHC molecules. The peptide–class I MHC complexes then move through the Golgi complex to the cell surface.



MHC- I

MHC-II



MHC-I

- Heavy chain (alpha) and "microglobulin" (beta two)
- Heavy is 45 kDa, has three domains + a transmembrane component (40 aa) + a cyto- plasmic tail (30 aa)
- The three alpha domains are called: α1, α2, & α3
- α1 and α2 interact to present processed Ag
- Process Ag is optimally a nonomer

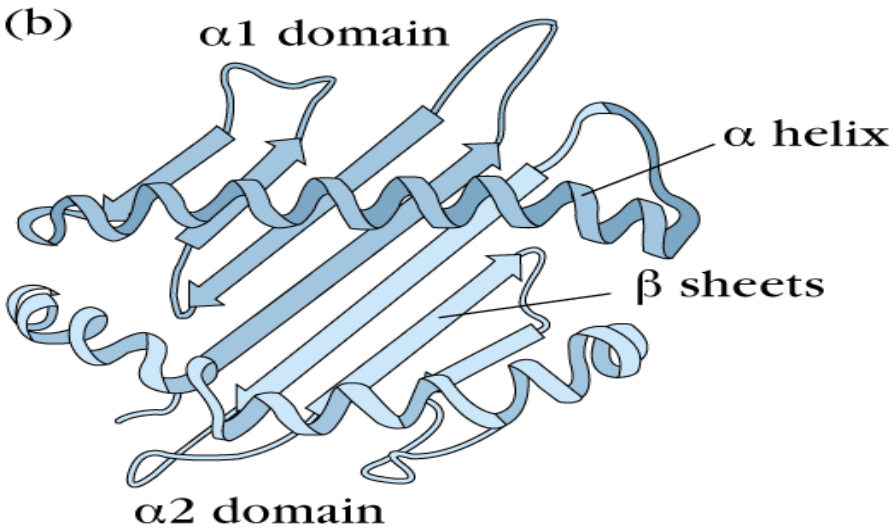
- Microglobulin (12 kDa) associates non-covalently with α3
- Microglobulin and α3 are part of immunoglobulin superfamily
- Microglobulin is the only member of the superfamily that does not have a component linking it to a membrane

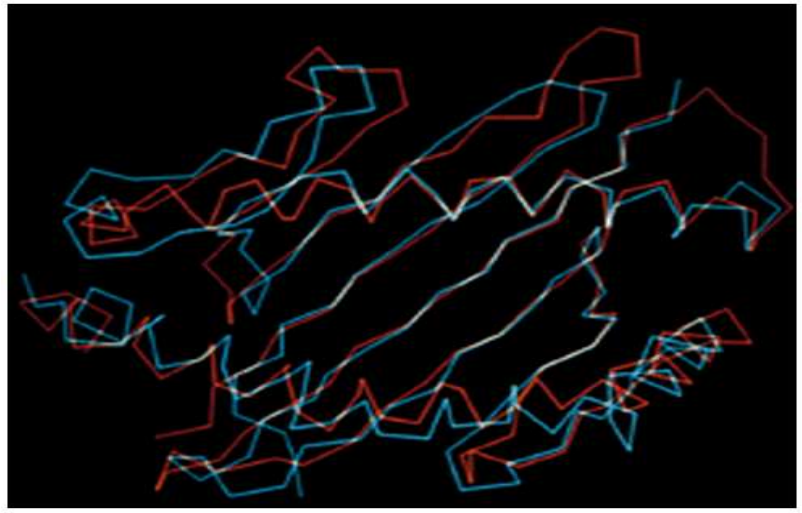
MHC-II

- An alpha and beta chain, 33 kDA and 28 kDa, respecitvely.
- Chains are non-covalently associated.
- Each chain has two domains.
- α1-β1 interact to present processed Ag
- Processed Ag is optimally 13-18 aa
- α2 & β2 are part of immunoglobulin super family

The “cleft”… where processed Ag is presented

Composed of two alpha helices plus eight beta sheets





“Two bananas on a plate”

MHC-I: α1-α2

MHC-II: α1-β1

Clefts can be superimposed; thus, two **genetic solutions** to a common need

Simplified organization of the MHC

- ✓ The MHC is referred to as the H-2 complex in mice and as the HLA complex in humans.
- ✓ In both species the MHC is organized into a number of regions encoding class I (pink), class II (blue), and class III (green) gene products.
- ✓ The class I and class II gene products shown in this figure are considered to be the classical MHC molecules.
- ✓ The class III gene products include complement (C) proteins and the tumor necrosis factors (TNF-α and TNF-β).
- ✓ MHC is attributed to **polygenecity, polymorphism**, **co-dominance**, and **linkage disequilibrium**
- ✓ There are no **rearrangement**s!

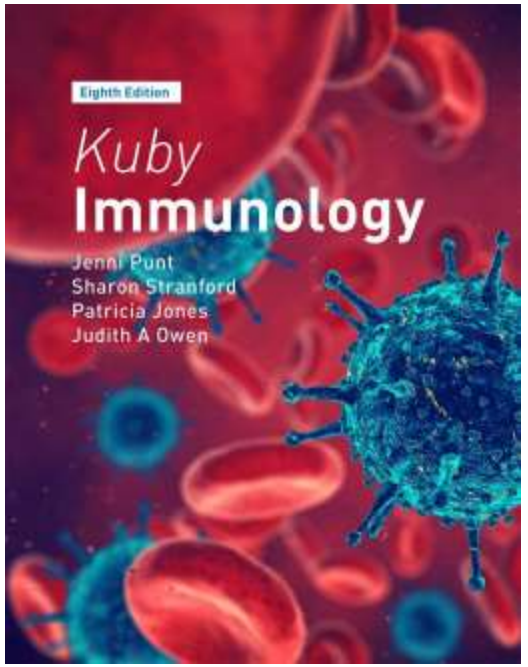
Mouse H-2 complex

Complex	H-2						
MHC class	I	II		III		I	
Region	K	IA	IE	S		D	
Gene products	H-2K	IA αβ	IE αβ	C′ proteins	TNF-α TNF-β	H-2D	H-2L

Human HLA complex

Complex	HLA							
MHC class	II			III		I		
Region	DP	DQ	DR	C4, C2, BF		B	C	A
Gene products	DP αβ	DQ αβ	DR αβ	C′ proteins	TNF-α TNF-β	HLA-B	HLA-C	HLA-A

Acknowledgement



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