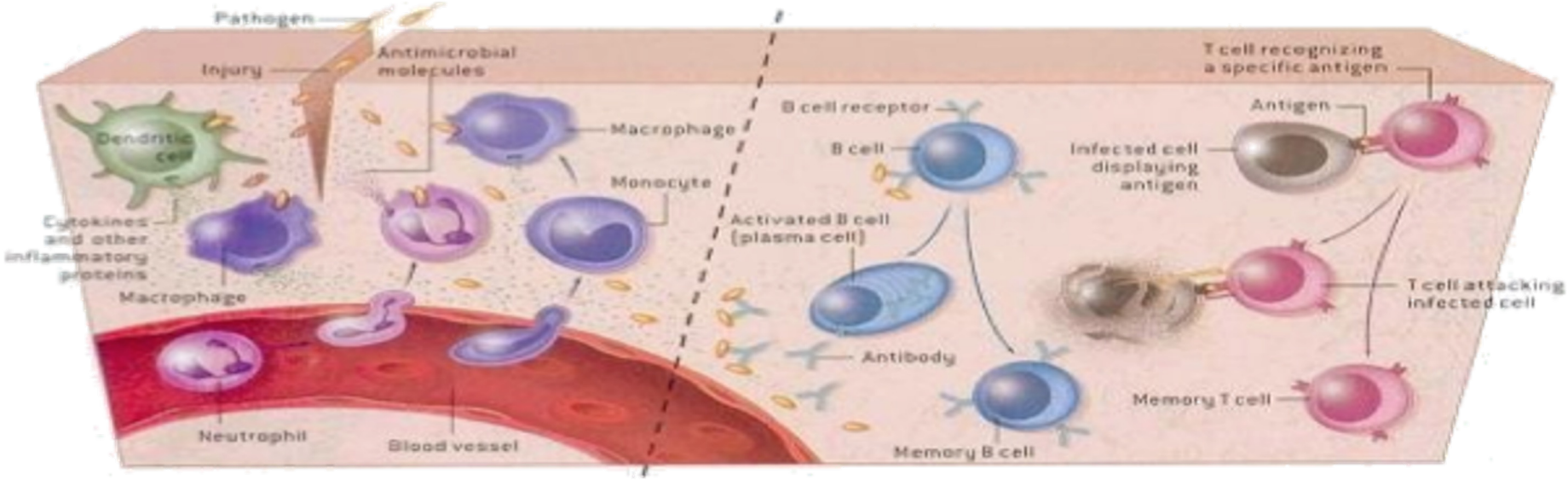
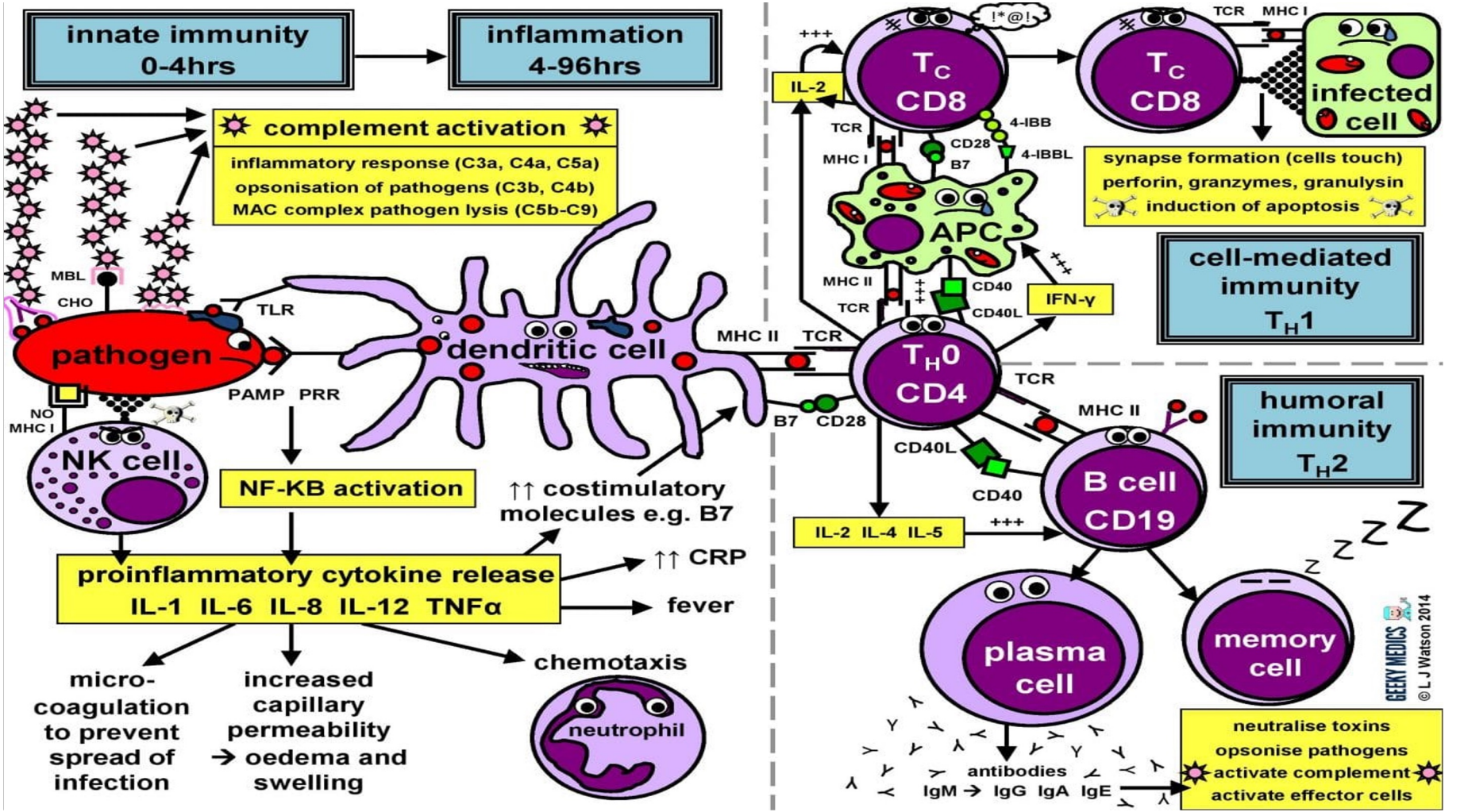
Immunogenetics &
The Histocompatibility Complex

Overview of the Immune Response

Innate Immune System	Adaptive Immune System
Response is non-specific	Pathogen and antigen specific response
Exposure leads to immediate response	Lag time between exposure and maximal response
No immunological memory	Exposure leads to immunological memory
Found in nearly all forms of life	Found only in jawed vertebrates




innate immunity
0-4hrs
inflammation
4-96hrs
complement activation
inflammatory response (C3a, C4a, C5a)
opsonisation of pathogens (C3b, C4b)
MAC complex pathogen lysis (C5b-C9)
MBL
CHO
pathogen
TLR
PAMP
PRR
dendritic cell
NO MHC I
NK cell
NF-KB activation
↑↑ costimulatory molecules e.g. B7
proinflammatory cytokine release
IL-1 IL-6 IL-8 IL-12 TNFα
↑↑ CRP
fever
chemotaxis
neutrophil
micro-coagulation to prevent spread of infection
increased capillary permeability → oedema and swelling
+++
IL-2
!*@!
TC CD8
TCR
MHC I
4-IBB
CD28
B7
4-IBBL
APC
MHC II
CD40
CD40L
IFN-γ
TH0 CD4
B7
CD28
IL-2 IL-4 IL-5
TC CD8
infected cell
synapse formation (cells touch)
perforin, granzymes, granulysin
induction of apoptosis
cell-mediated immunity
TH1
humoral immunity
TH2
B cell CD19
plasma cell
memory cell
antibodies
IgM → IgG IgA IgE
neutralise toxins
opsonise pathogens
activate complement
activate effector cells
GEEKY MEDICS
© L J Watson 2014

The Major Histocompatibility Complex (MHC)

General organization and inheritance of the MHC

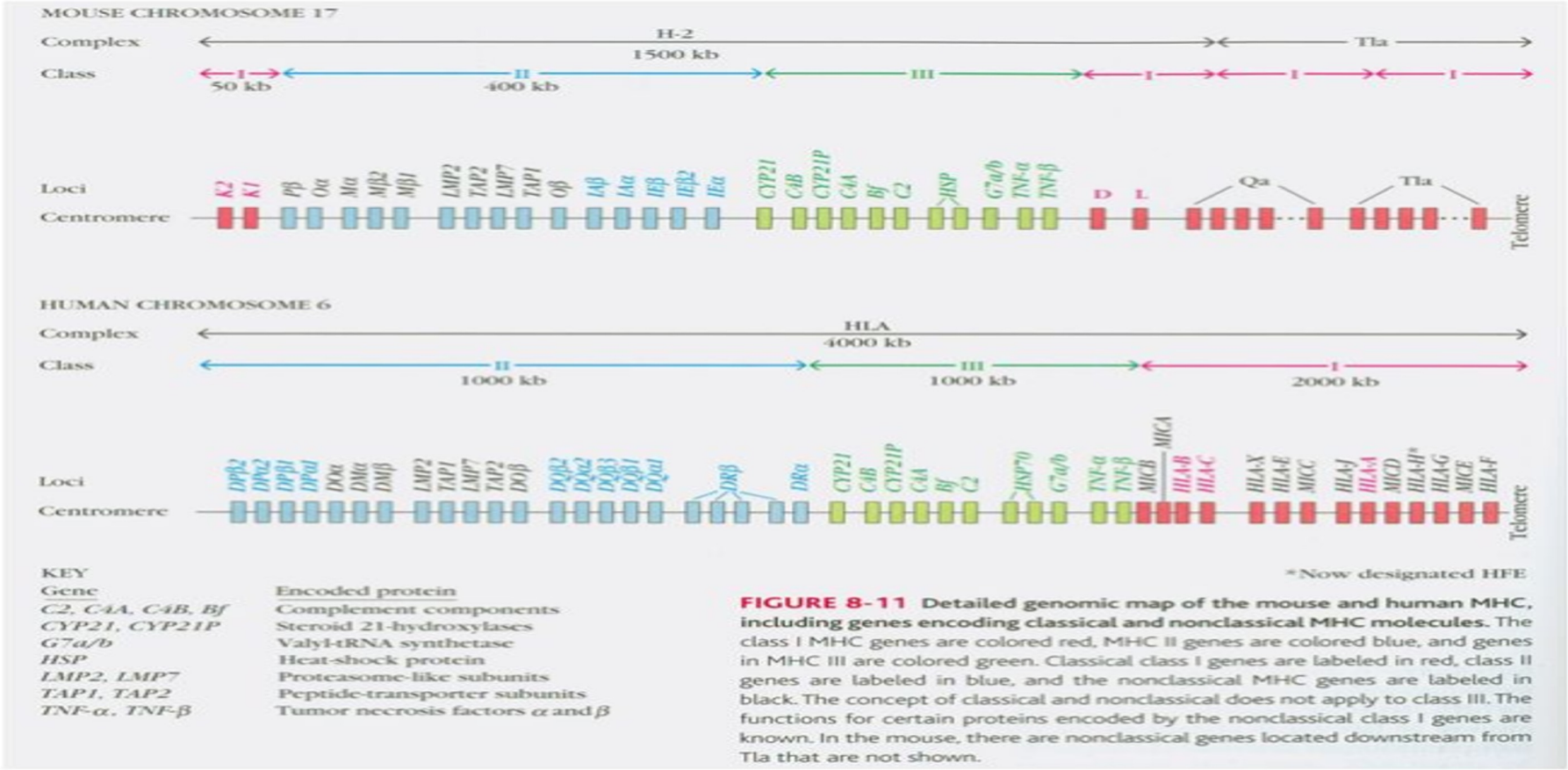
- Every mammalian species studied to date possess the tightly linked cluster of genes that constitute the MHC, whose products play roles in intercellular recognition and in discrimination between self and nonself.
- The MHC participates in the development of both humoral and cell-mediated immune responses. Studies of this gene cluster originated when it was found that the rejection of foreign tissue is the result of an immune response to cell surface molecules, now called histocompatibility antigens.
- In the mid-1930s, Peter Gorer, who was using inbred strains of mice to identify blood-group antigens, identified four groups of genes, designated I through IV, that encoded blood-cell antigens.
- Work carried out in the 1940s and 1950s by Gorer and George Snell established that antigens encoded by the genes in the group designated II took part in the rejection of transplanted tumors and other tissue. Snell called these genes "histocompatibility genes"; their current designation as histocompatibility-2 (H-2) genes was in reference to Gorer's group II blood-group antigens.
- Although Gorer died before his contributions were recognized fully, Snell was awarded the Nobel prize in 1980 for this work.

The MHC encodes three major classes of molecules

The **major histocompatiblity 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 **HLA complex in humans** and as the H-2 complex in mice. 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:

- **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 peptide antigens to T_c cells.**
- **Class II MHC encode** glycoproteins expressed primarily on antigen-presenting cells (macrophages, dendritic cells, and B cells), where they **present processed antigenic peptides to T_H cells**.
- **Class III MHC genes encode**, in addition to other products, various secreted proteins that have immune functions, **including components of the complement system and molecules involved in inflammation**.

Detailed genomic map of MHC gene



KEY

Gene	Encoded protein
C2, C4A, C4B, Bf	Complement components
CYP21, CYP21P	Steroid 21-hydroxylases
G7a/b	Valyl-tRNA synthetase
HSP	Heat-shock protein
LMP2, LMP7	Proteasome-like subunits
TAP1, TAP2	Peptide-transporter subunits
TNF-α, TNF-β	Tumor necrosis factors α and β

*Now designated HFE

FIGURE 8-11 **Detailed genomic map of the mouse and human MHC, including genes encoding classical and nonclassical MHC molecules.** The class I MHC genes are colored red, MHC II genes are colored blue, and genes in MHC III are colored green. Classical class I genes are labeled in red, class II genes are labeled in blue, and the nonclassical MHC genes are labeled in black. The concept of classical and nonclassical does not apply to class III. The functions for certain proteins encoded by the nonclassical class I genes are known. In the mouse, there are nonclassical genes located downstream from Tla that are not shown.

Simplified organization of the MHC in the mouse and human

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*

*Not present in all haplotypes

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

Schematic diagrams of a class I and a class II MHC genes, mRNA transcripts, and protein molecules

Organization of Class I MHC Genes

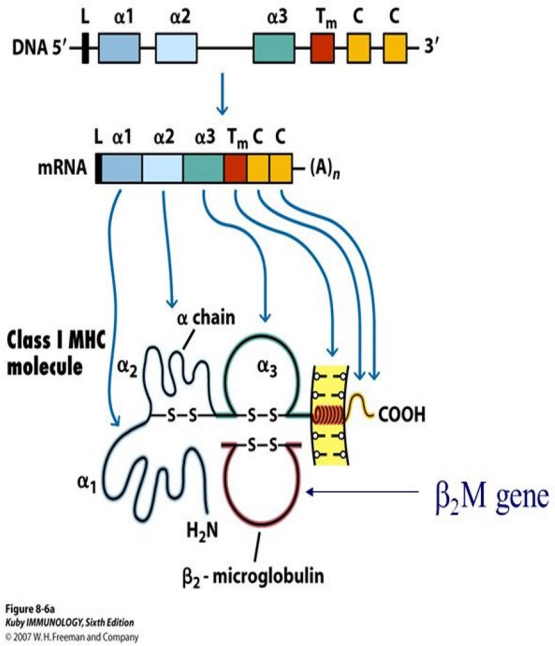
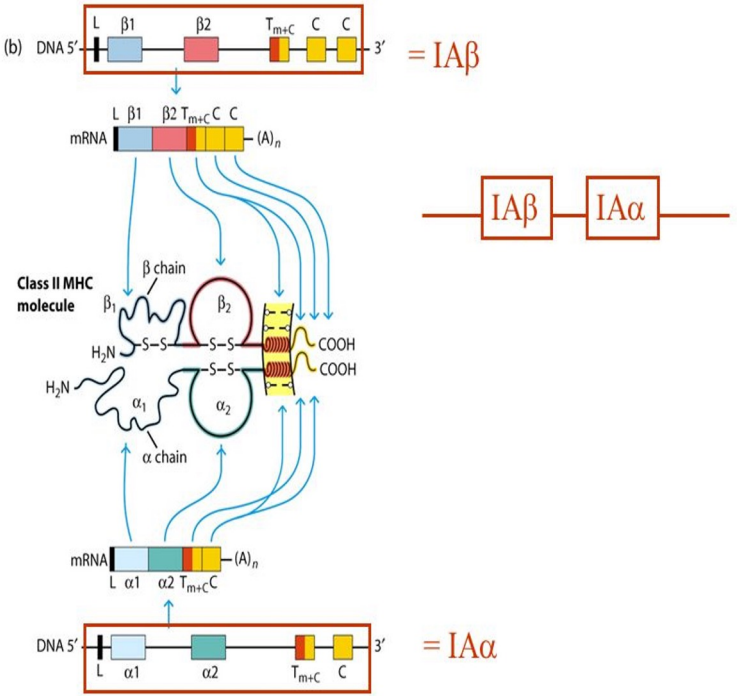
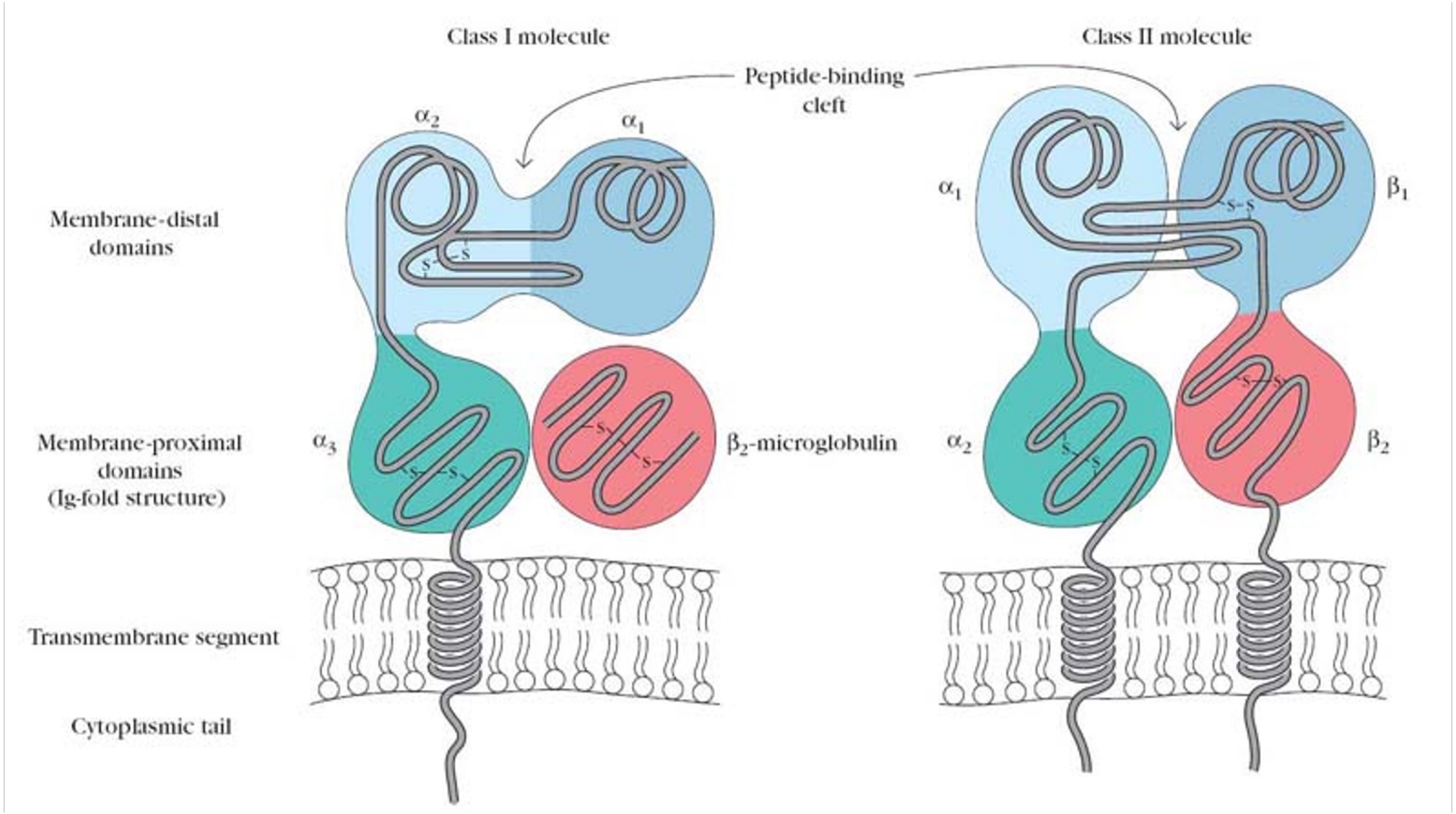


Figure 8-6a
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company

Organization of Class II MHC Genes

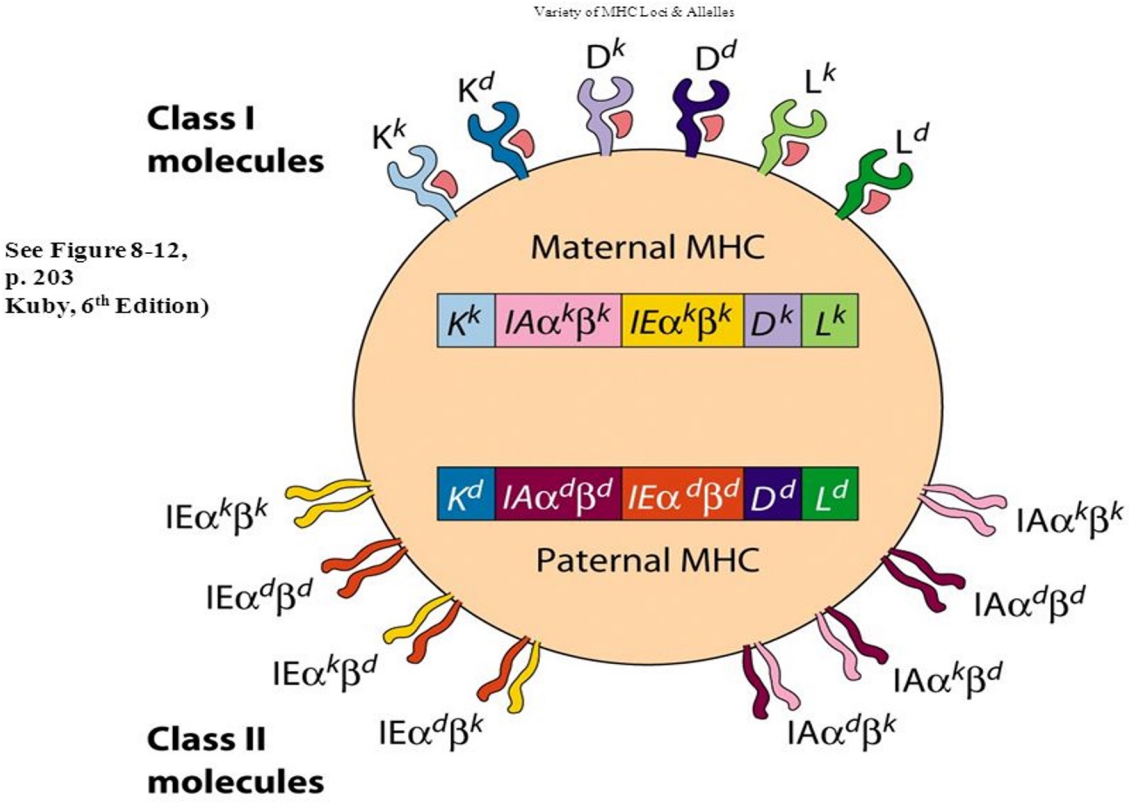


Schematic diagrams of a class I and a class II MHC molecule



Polymorphism of Class I and Class II Molecules in Human HLA

Cellular expression of MHC molecules



See Figure 8-12, p. 203 Kuby, 6th Edition)

Key Terms

- **Allele**: An allele is a variation form of a gene.

- **Epitope**: That part of a biomolecule (for example a protein) that is the target of an immune response.

- **Polygenic**: Having an limitless number of derivatives at a point.

- **Haplotype**: Set of alleles present in each parental chromosome (two sets).

Key Points

- The MHC genes are highly polymorphic; because of this there are many different alleles in the different individuals inside a population.

- The evolution of the MHC polymorphism undertakings that a population will now not succumb to a new pathogen or a mutated one, due to the fact some individuals will be capable of develop an adequate immune response to success over the pathogen.

- MHC molecules display a molecular fraction called an epitope and mediate interactions of leukocytes with other leukocytes or body cells.

MHC gene family

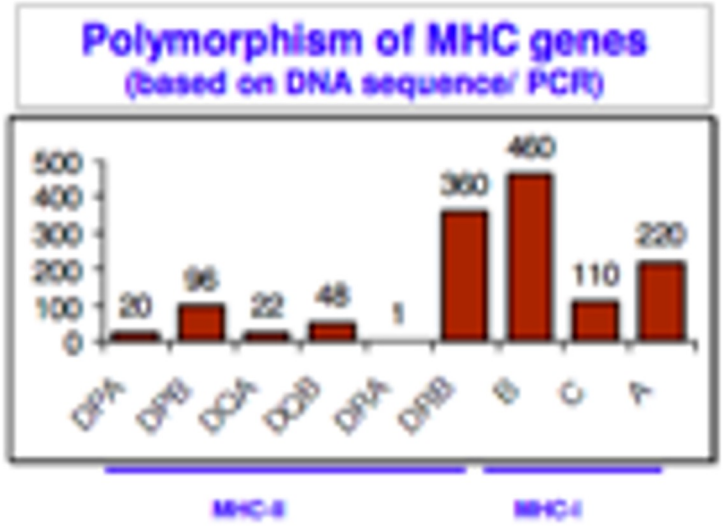
The MHC gene family is attained in multiple ways:

1. The MHC's genetic encoding is polygenic,

2. MHC genes are highly polymorphic and have many variants,

3. Several MHC genes are expressed from both inherited alleles (variants).

- MHC gene families are found in all vertebrates, though they vary widely. Chickens have among the smallest known MHC regions (19 genes).



Humans:

HLA Class-I genes: A (240), B (470), C (110) alleles (1.2×10^7)

HLA Class-II genes:

DP= DPB1 (96), DPA1 (20) alleles

DQ= DQA1 (22), DQB1 (49) alleles

DR= DRB1 (304) alleles = 1.8×10^{10} different Class II combinations, and

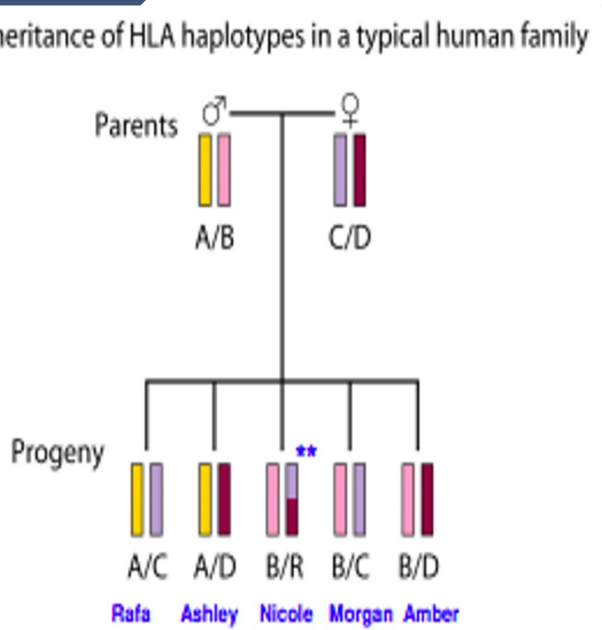
$(1.2 \times 10^7) \times (1.8 \times 10^{10}) = 2.25 \times 10^{17}$ different combinations of Class I and Class II possible combinations

MHC haplotype

- The set of alleles is found in every chromosome is called MHC haplotype. In humans, each HLA
allele is heterozygous individual have two MHC haplotypes, one in each chromosome (considered one of paternal origin and the other is maternal origin).

- The MHC genes are highly polymorphic; which is mean that there are many different alleles in the different individuals inside a population.

- The polymorphism is so high that combined in population (non-endogamic) there aren't two individuals with match the same set of MHC genes and molecules, except identical twins.



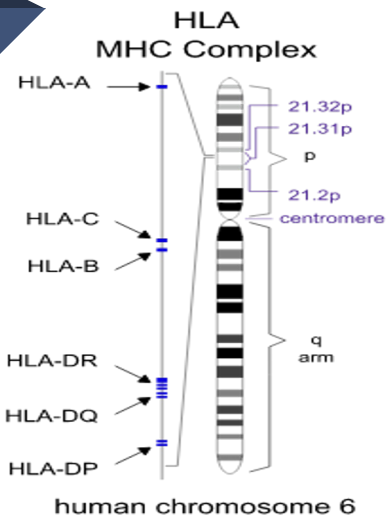
HLA MHC complex

- Located of The polymorphic regions in each allele are in the region for peptide contact, that is going to be displayed to the lymphocyte.

- Due to that, the contact region for each allele of MHC molecule is highly variable, as the polymorphic residues of the MHC will make specific clefts in which only certain types of residues of the peptide can enter.

- This force a very specific link between the MHC molecule and the peptide, and it mean that each MHC variant will be able to bind specifically only those peptides that are able to precisely enter in the cleft of the MHC molecule, which is variable for each allele.

- The MHC molecules have a broad specificity, because they can bind many, but not all, types of possible peptides.



HLA MHC complex: The human leukocyte antigen (HLA) system is the name of the major histocompatibility complex (MHC) in humans. The super locus contains a large number of genes related to immune system function in humans. This group of genes resides on chromosome 6, encodes cell-surface antigen-presenting proteins and has many other functions.

Processing Antigen Presentation by MHCs

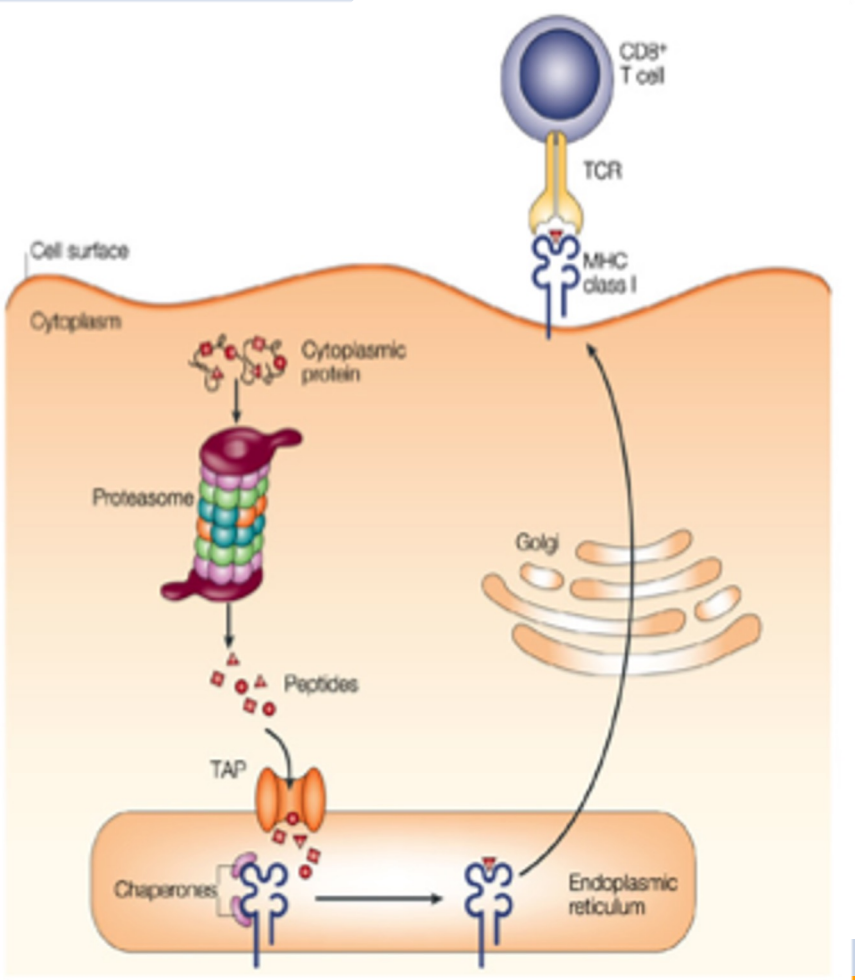
Processing of antigen presentation by MHC I

- The assembly of MHC I molecules occurs in the endoplasmic reticulum of cells.

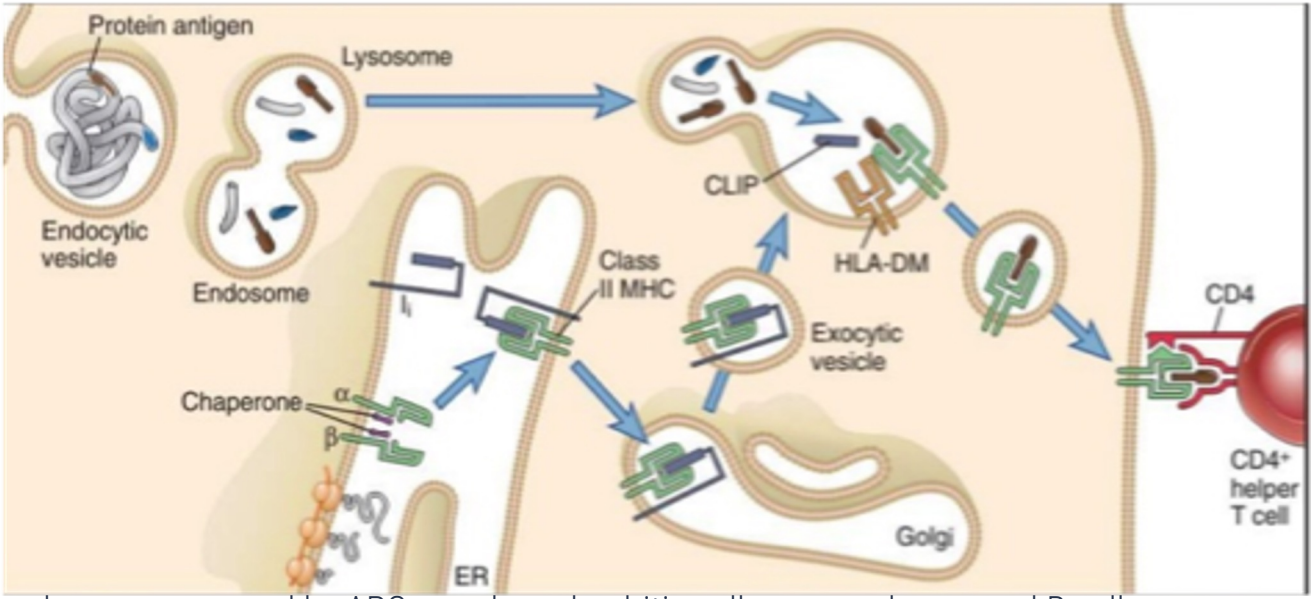
- The role of MHC I stimulating Tc cells which eliminate a number of foreign viral antigens and self– antigens with foreign peptides.

Processing of antigen presentation by MHC I

- MHC I molecules bind small viral peptides that are degraded by proteasomes.
- These small viral peptides are moved into the lumen of the ER through the transporter associated with antigen processing (TAP) complex.
- With the help of chaperone proteins, such as tapasin, ERp57, and calreticulin, the peptides are loaded onto MHC I molecules.
- The peptide-loaded MHC I is then transferred to the surface of the cell via the Golgi apparatus and vesicular transport.
- Once at the cell surface, MHC I molecules display their antigen cargo to Tc cells.

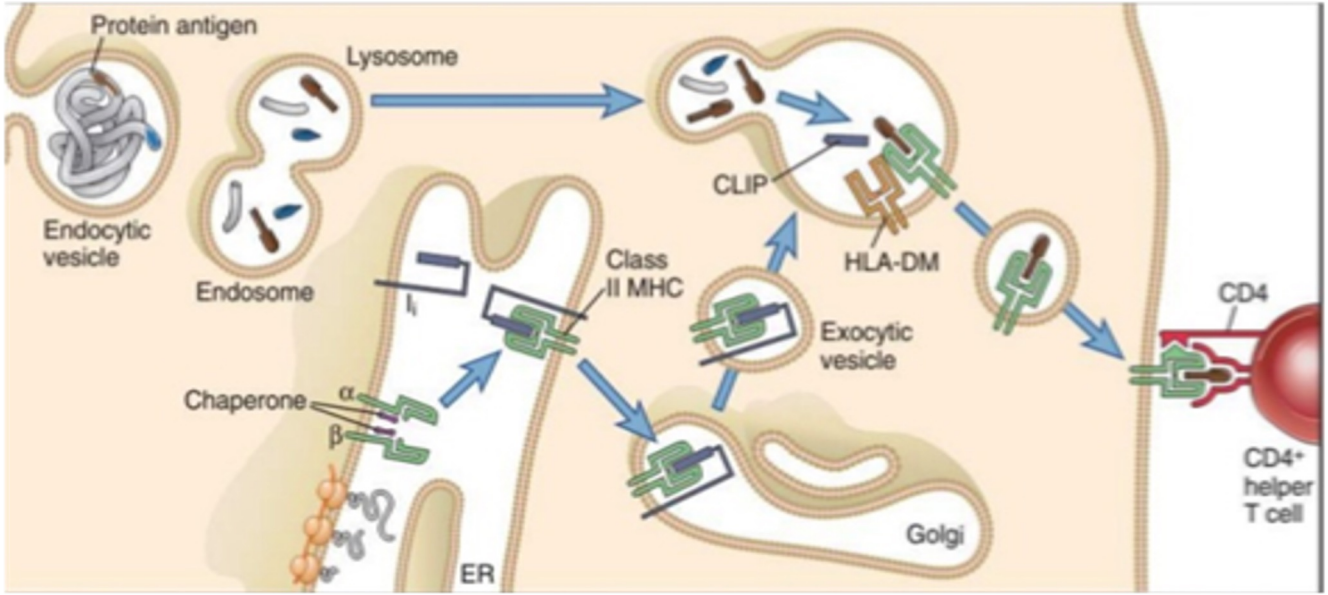


Processing of antigen presentation by MHC II



- MHC class II molecules are expressed by APCs, such as dendritic cells, macrophages and B cells.
- MHC class II molecules bind to peptides that are derived from proteins degraded in the endocytic pathway.
- MHC class II complexes are assembled in the ER and are stabilized by invariant chain (Ii).
- The complex of MHC class II and Ii is transported through the Golgi into a compartment which is termed the MHC class II compartment.

- Due to acidic pH, proteases cathepsin S and cathepsin L are activated and digest Ii, leaving a residual class II-associated Ii peptide (CLIP) in the peptide-binding groove of the MHC class II.
- Later, the CLIP is exchanged for an antigenic peptide derived from a protein degraded in the endosomal pathway.
- This process requires the chaperone HLA-DM, and, in the case of B cells, the HLA-DO molecule.
- MHC class II molecules loaded with foreign peptide are then transported to the cell membrane to present their cargo to CD4+ T cells.



Processing of antigen presentation by MHC I and MHC II

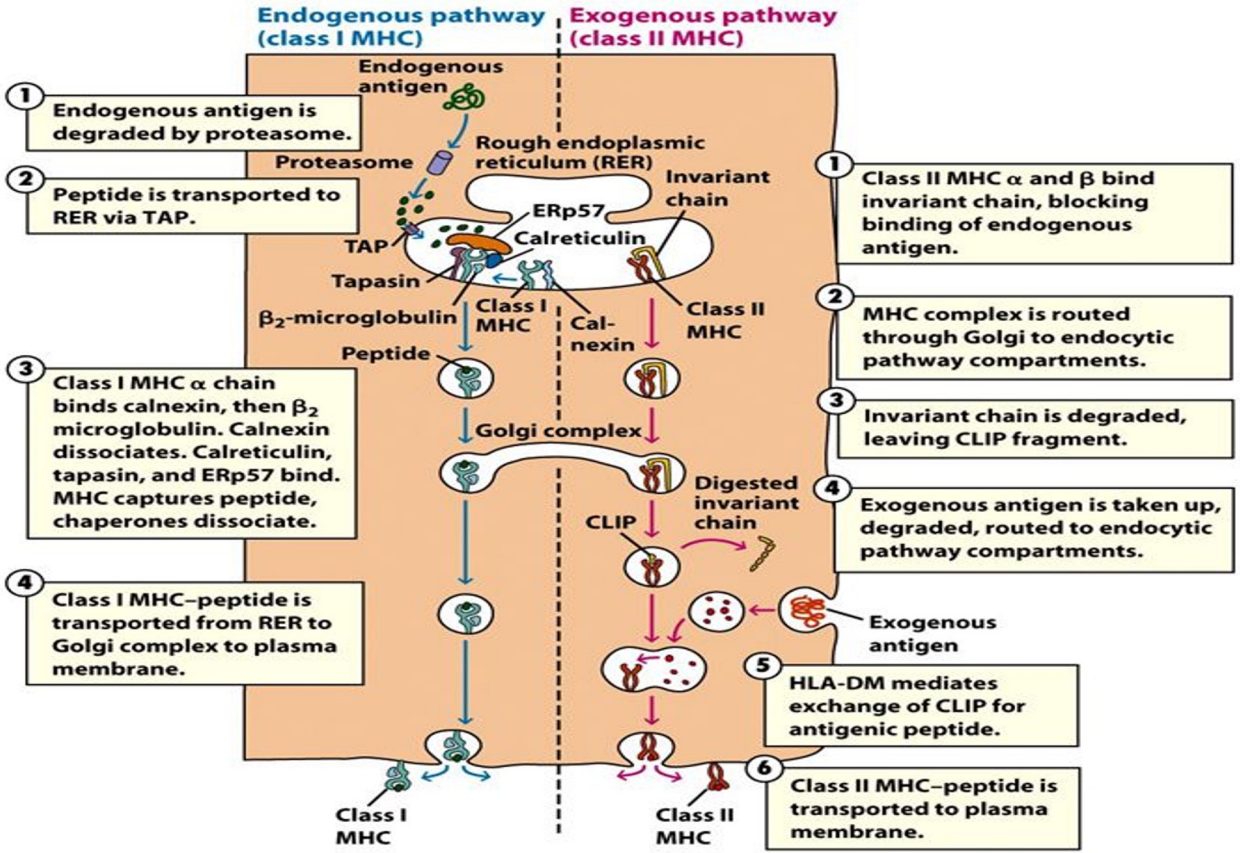


Figure 8-23
Kuby IMMUNOLOGY, Sixth Edition

Summary of Class I and II MHC Pathways

Feature	Class II MHC Pathway	Class I MHC pathway
Composition of stable peptide-MHC complex	Polymorphic a and b chains, peptide 	Polymorphic a chain, b_2-microglobulin, peptide 
Types of APCs	Dendritic cells, mononuclear phagocytes, B lymphocytes; endothelial cells, thymic epithelium	All nucleated cells
Responsive T cells	$CD4^+$ T cells	$CD8^+$ T cells
Source of protein antigens	Endosomal/lysosomal proteins (mostly internalized from extracellular environment)	Cytosolic proteins (mostly synthesized in the cell; may enter cytosol from phagosomes)
Enzymes responsible for peptide generation	Endosomal and lysosomal proteases (e.g., cathepsins)	Cytosolic proteasome
Site of peptide loading of MHC	Specialized vesicular compartment	Endoplasmic reticulum
Molecules involved in transport of peptides and loading of MHC molecules	Chaperones in ER; invariant chain in ER, Golgi and MIIC/CIIV; DM	Chaperones, TAP in ER

Abbreviations: APC, antigen-presenting cell; CIIV, class II vesicle; ER, endoplasmic reticulum; MHC, major histocompatibility complex; MIIC, MHC class II compartment; TAP, transporter associated with antigen processing

Immunogenetics

MHC in Graft Rejection

•**Allograft** is a graft between genetically different members of the same species (e.g., from one human to another). Allografts are usually rejected unless the recipient is given immunosuppressive drugs. The severity and rapidity of the rejection will vary depending on the degree of the differences between the donor and the recipient at the MHC loci.

Unless immunosuppressive measures are taken, allografts are rejected by a process called the **allograft reaction**.

- The acceptance or rejection of a transplant is determined, in large part, by the class I and class II MHC proteins on the donor cells.
- The proteins encoded by the **DR locus** of class II are especially important. These donor alloantigens activate recipient T cells, both helper and cytotoxic, which bear T-cell receptors specific for the alloantigens.
- The activated T cells proliferate and then react against the alloantigens on the donor cells. CD8+ cytotoxic T cells do most of the killing of the allograft cells.
- Foreign MHC proteins typically activate many more T cells (i.e., they elicit a much stronger reaction) than do foreign proteins that are not MHC proteins.

•The strength of the response to foreign MHC proteins can be explained by the two processes by which the recipient's immune response is stimulated.

These processes are as follows:

Direct Pathway:

- The **direct process** in which the donor's antigen-presenting cells (APC) from the graft can present either the donor's or the recipient's proteins in association with their class I and class II MHC proteins and activate the recipient's immune response in the draining lymph node. This process results in activation of the recipient's cytotoxic T cells that kill the cells of the graft. This is the main mechanism of the **acute graft rejection** process. The recipient's proteins can be recognized as foreign by the recipient's immune cells when presented by a foreign MHC protein.

Indirect Pathway:

- The **indirect process** in which the recipient's antigen-presenting cells present the donor's proteins. The donor's self proteins and class I and class II MHC proteins can be shed and subsequently processed by the recipient's APC that enter the graft. The APC then migrates to the draining lymph node where it activates the recipient's helper T cells and B cells. This process typically results in production of antibodies against the graft and is thought to be important in the **chronic rejection** process.

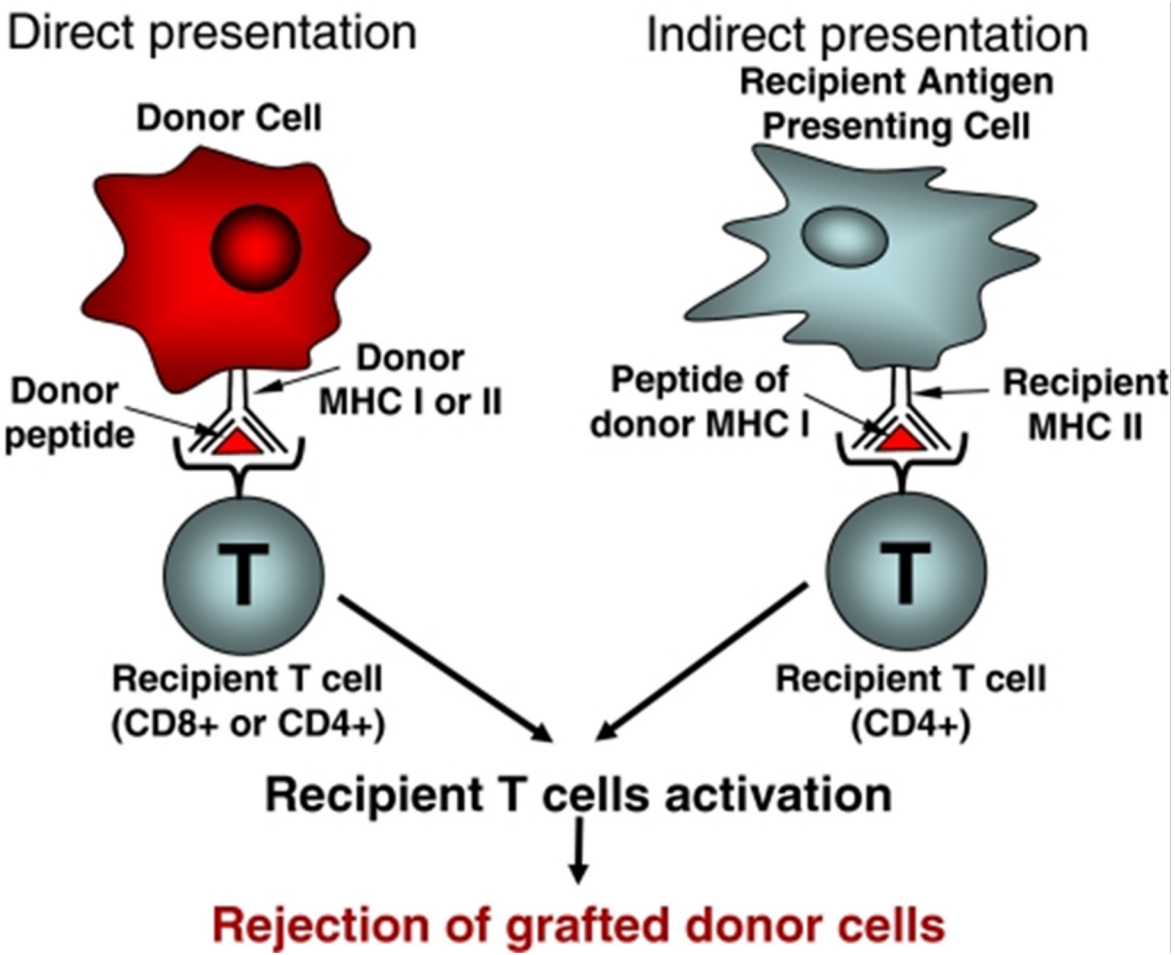


Figure: Schematic representation of direct and indirect recognition of donor antigens to the recipient T cells

Prevention and treatment of allograft rejection:

- Reducing the immunogenicity of allografts.
  - HLA typing of the recipient and the donor.
  - Screening of HLA antibodies in the recipient.
  - Cross-matching.

- Immunosuppression.
  - To reduce the rejection of transplanted tissue, immunosuppressive measures are used (e.g., cyclosporine, tacrolimus, corticosteroids, azathioprine, etc).

The fetus is an allograft that is not rejected:

- A fetus has MHC genes inherited from the father that are foreign to the mother, yet allograft rejection of the fetus does not occur. This is true despite many pregnancies from the same mother–father combination that produce offspring with the same MHC haplotypes.
- The mother forms antibodies against the foreign paternal MHC proteins; therefore, the reason is not that the mother is not exposed to fetal antigens. One possible explanation is that the trophoblast layer of the placenta does not allow maternal T cells to enter the fetus.

MHC association with Diseases

- A number of diseases have been found to occur at a higher frequency in individuals with certain MHC haplotypes.

Infectious Diseases

- HIV infection (AIDS acquired immunodeficiency syndrome)
- Dengue shock syndrome
- Hepatitis B virus infection (HBV)
- Hepatitis C virus infection (HCV)
- Human papillomavirus virus infection (HPV)
- Leprosy
- Tuberculosis (TB)
- Leishmaniasis

Autoimmune Diseases

- Ankylosing spondylitis (AS)
- Crohn's disease (CD)
- Celiac disease (CeD)
- Dermatomyositis (DM)
- Multiple sclerosis (MS)
- Psoriasis (Ps)
- Rheumatoid arthritis (RA)
- Systemic lupus erythematosus (SLE)
- Type 1 diabetes (T1D)

Relationship between the MHC variants involved in autoimmune and infectious diseases

- Both autoimmune and infectious diseases seem to involve certain MHC classes, and only a few MHC alleles are shared between these two distinct disease groups.
  - ❖ Two hypotheses have been proposed to explain the relationship between the MHC variants involved in both groups of diseases.
    - ➢ The first, known as the “pathogen driven selection” hypothesis, states that pressure exerted on the human genome by pathogens has led to the advantageous selection of host defense genes and, subsequently, to much higher polymorphism in the MHC.
    - ➢ The second hypothesis states that pathogens can trigger autoimmunity, as suggested by epidemiological studies.

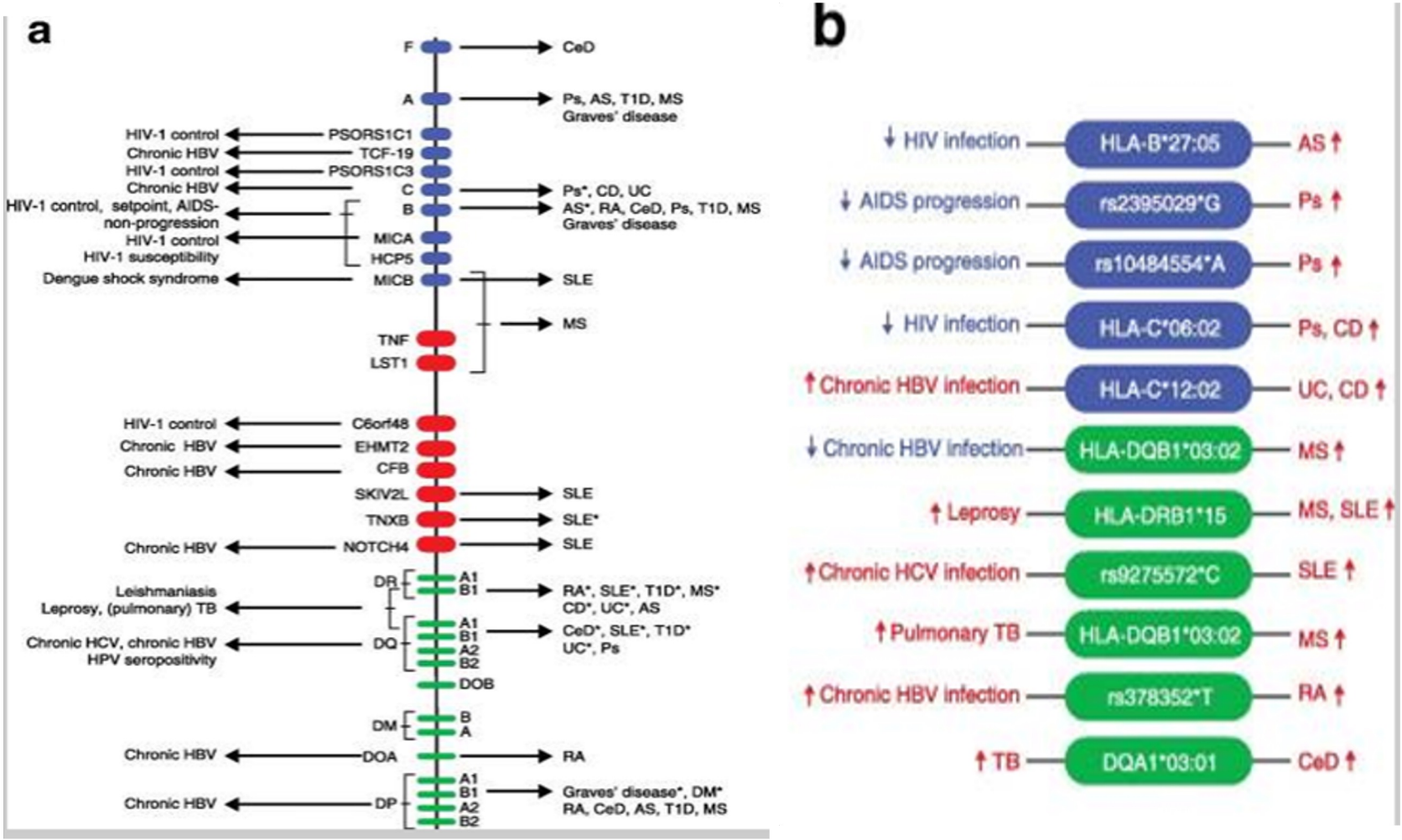


Figure: Major histocompatibility complex allele associations with autoimmune and infectious diseases.