UNIT-4

Disease & Immune response: - Infectious diseases, hypersensitivity - Types I, II, III and IV; autoimmune disorder; immunodeficiency diseases. Tumour and transplantation immunology - Major histocompatibility complex (MHC), immunotherapy for the treatment of cancer.

Immune deficiency diseases

Immune deficiency diseases:

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- Deficiencies of host defense systems result in an immunologic imbalance that can lead to a susceptibility to infection, an autoimmune disease, or a predisposition to malignancies

- It is the absence or failure of normal function of one or more elements of the immune system Known as immunodeficiency disease

- It Can be specific or non specific

  - ✓ Specific = Abnormalities of B & T cells
  - ✓ Non specefic = Abnormalities of non specific components

Types of immunodeficiency disorders:

1.Primary: Causes in immune system component:

a. According of component:

- ✓ Complements
- ✓ Phagocytic
- ✓ B cells.
- ✓ T Cells.

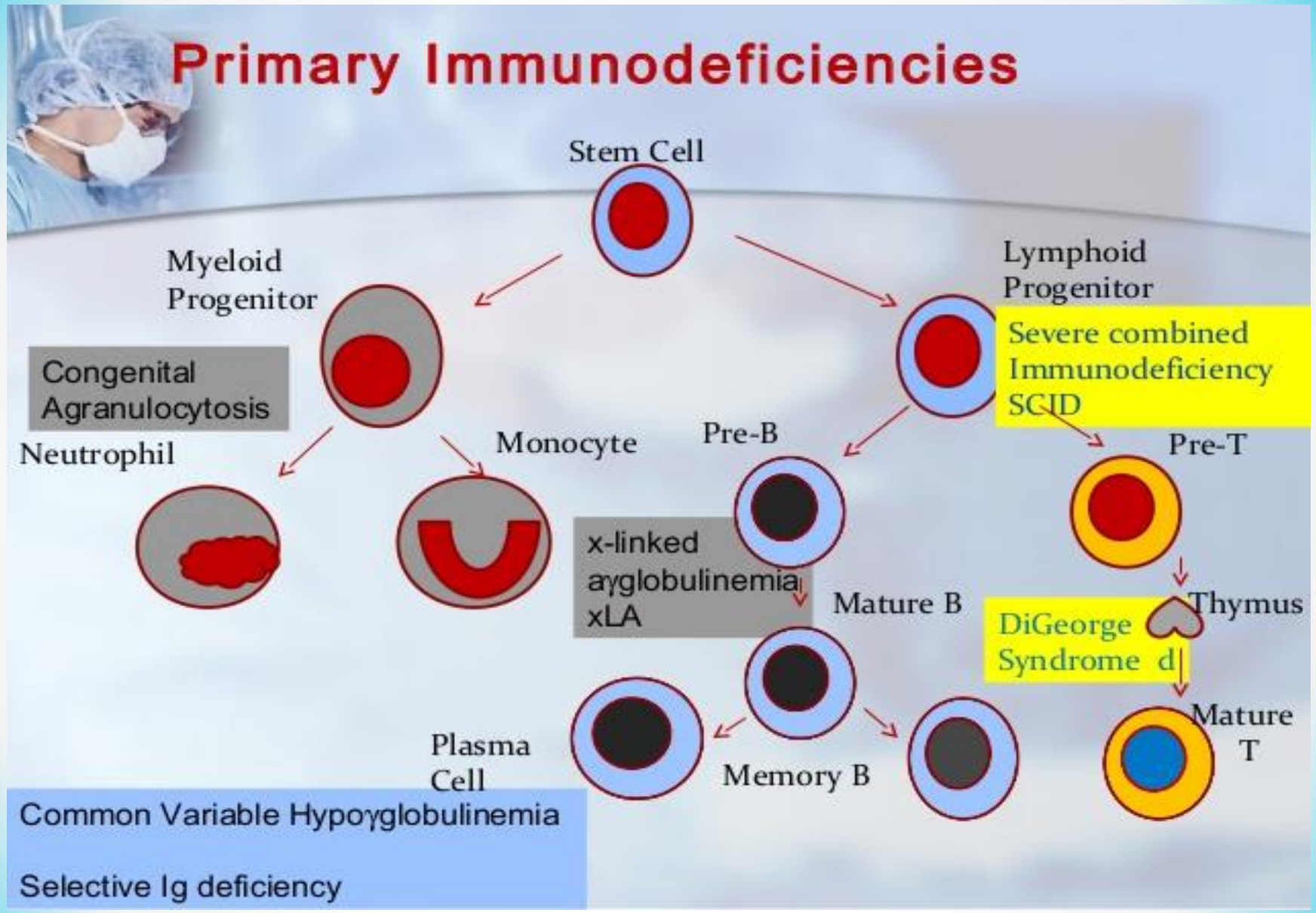
b. According to the etiology:

- ✓ Congenital (X-linked disease)
- ✓ Acquired (AIDS)
- ✓ Embryogenesis (Digoerge syndrome).
- ✓ Idiopathic

2- Secondary: Non Immunogenic causes:

a. Prematurity.
b. Mal nutrition.
c. Malignancy.
d. Injury, Burns, Splenectomy.
e. Drugs.

Primary Immunodeficiencies



Primary immunodeficiencies

- Primary immunodeficiencies are inherited defects of the immune system
- These defects may be in the specific or nonspecific immune mechanisms
- They are classified on the basis of the site of lesion in the developmental or differentiation pathway of the immune system

B-cell deficiency disorders:

- Causative agents are most commonly extracellular organisms, namely pyogenic and enteric bacteria, because patients are deficient in serum opsonins (antibodies) necessary for phagocytosis.

- Patients with IgA deficiency or common variable hypogammaglobulinemia are by *Giardia lamblia* parasite.

- Sites of infection include the skin, sinuses, meninges, and the respiratory, urinary, and gastrointestinal tracts

Disorder	Clinical Features	Therapy
1- X-linked agammaglobu-linemia (Bruton disease)	Recurrent pyogenic infections; infections of lungs, sinuses, middle ear, skin, central nervous system	Immune serum globulin; antibiotics
2-Transient hypogamma-globulinemia of infancy (1st 3 years of life)	Recurrent pyogenic infections; frequent in families with other immunodeficiencies	Antibiotics; immune serum globulin (selected patients)
3-Selective immuno-globulin deficiency (IgA, IgM, IgG sub classes)	Recurrent infections of lungs, sinuses; gastrointestinal disease; allergy; frequent in families with common variable immunodeficiencies	Antibiotics; immune serum globulin (IgG subclass deficiencies only)
4-Immunoglobulin defi-ciency with increased IgM (and IgD)	Infections of lungs, sinuses, middle ear; increased frequency of autoimmune disease Ectodermal displasea	Immune serum globulin; antibiotics
5-Common variable immunodeficiency	Infections of lungs, sinuses, middle ear; giardiasis; malabsorption; autoimmune disease	Immune serum globulin; antibiotics

T-cell deficiency disorders

- It also known as cell-mediated (cellular) immuno-deficiencies, result from abnormalities in T-cell functions.
- Recurrent infections --Causative agents are intracellular pathogens (e.g., herpesviruses, mycobacteria, fungi *{Candida}*, and protozoa *{Pneumocystis carinii*, *Toxoplasma}*.
- Congenital cell-mediated immunodeficiencies: defects in lymphoid stem cell differentiation, which result in severe combined immunodeficiency disorders.
- Sites of infection include a variety of sites, both local and systemic.

Disorder	Clinical Features	Therapy
*Severe combined immuno deficiency	Recurrent infections; chronic diarrhea; failure to thrive: graft versus host disease, anemia	Bone marrow transplantation Antibiotics and IVIG
Defects of the purine sal vage pathway -Adenosine deaminase deficiency -Purine nucleoside phosphorylase deficiency	Recurrent infections; dysostosis (adenosine deaminase deficiency); anemia and mental retardation (purinenucleoside phosphorylase deficiency) Rib and Scapula abnormality in ADA	Bone marrow transplan tation; enzyme replacement therapy
*DiGeorge anomaly (third and fourth pouch/arch syndrome)	Hypoparathyroidism (hypocalcemia); facial abnormalities; cardio vascular abnormalities; infections; mental deficiency (some patients); gastrointestinal tract malformation (some patients).	Thymus graft or thymosin therapy)
*Chronic mucocutaneous candidiasis	Chronic candidal infection of the skin, nails, scalp, and mucous membranes; autoimmune endocrine disorders Intestinal malabsorption recurrent infections	Topical and systemic antifungal agents; transfer factor; thymus transplantation
*Ataxia-telangiectasia	Oculocutaneous telangictasia; progressive cerebellar ataxia; bronchiectasis, malignancy; defective chromosomal repair; raised a-fetoprotein	Bone marrow transplantation
*Wiskott-Aldrich syndrome	Eczema; thrombocytopenia; susceptibility to infections; malignancy; small, defective platelets	Bone marrow transplantation; antibiotics; splenectomy
*Short-limbed dwarfism Caltilage hair hypoplasia	Short-limbed dwarfism; lymphopenia	Immune serum globulin IVIG, Antibotics

Phagocyte Disorders

Affected individuals are prone to infections with *Staphylococcus aureus* and gram-negative enteric bacteria.

Disorder	Inheritance	Clinical Features	Therapy
1) Chronic granu-lomatous disease	X-linked (66%); autosomal recessive (33%)	Infections with catalase-positive bacteria and fungi affecting skin, lungs, liver; granuloma formation;	Antibiotics; γ-interferon
2)Myeloperoxidas deficiency	Autosomal Recessive	Fungal infections (candidiasis) in deep tissues, especially in presence of diabetes	Antibiotics
3)Leukocyte adhesion deficiency	Autosomal recessive	Delayed separation of the umbilical cord; skin infections; otitis media; pneumonia; gingivitis; periodontitis	Antibiotics
4)Abnormal chemotaxis -Hyper IgE -chediak-Higashi	Variable	Recurrent skin infections with staphylococci. enteric bacteria, Neuropathy, Occulo cultaneous albinism in chediak higashi	Antibiotics

Complement disorders

- Deficiency of early complement components (C1, C4, C2) results in systemic lupus erythematosus (SLE)] and increased susceptibility to pyogenic infections.

- C3 deficiency results in severe pyogenic infections. Several patients have also had SLE and glomerulonephritis.

- Deficiency of late complement components (C5, C6, C7, C8) results in systemic *Neisseria* infections

Diagnosis of immunodeficiency disease

Suspected cells has specific tests:

a. B-cells:

i. Total lg
ii. Selected lg A and lg G
iii. Anti A and Anti B
iv. Antibodies for pervious vaccination

b. T cells:

i. Lymphocyte count.
ii. Delayed hypersensitivity reaction for Tubrculin and Candida.
iii. T cells and macrophage function test.

c. Phagocyte:

i. Neutrophil count
ii. NBT test for screening.

d. Complement: Total and specific complement count.

Secondary immunodeficiency's

IMMUNODEGECIENCY CAUSED BY DRUGS

CORTICOSTEROIDS

- Cause changes in circulating leukocytes
- Depletion of CD4 cells
- Monocytopenia
- Decreased in circulating eosinophils and basophils
- Inhibition of T cell activation and B cell maturation
- Inhibit cytokine synthesis

METHOTREXATE

- Structural analogue of folic acid
- Blocks folic acid dependent synthetic pathways essential for DNA synthesis
- Prolonged use for treatment reduces immunoglobulin synthesis

CYCOLOSPORIN

- Have severe effects on T cell signaling and functions
- It binds to immunophilins which are believed to have a critical role in signal transduction
- Also inhibit IL 2 dependent signal transduction

OTHER CAUSES

- ✓ Malnutrition
- ✓ Minerals
- ✓ Vitamins
- ✓ Obesity

Major Histocompatibility Complex [MHC]

History

❖ Gorer (1930s):

1. Rejection of foreign tissue is the result of an immune response to cell-surface molecules.

2. Identification of I, II, III and IV groups of genes.

❖ Gorer and Snell (1940s & 1950s):

1. Antigens encoded by the genes in the group II took part inthe rejection of transplanted tumors and other tissues.

2. Snell called these genes “histocompatibility genes”(currently called H-2 genes)

3. Snell was awarded the Nobel Prize in 1980.Earlier studies were done in inbred strain of mice

Major Histocompatibility Complex

- Cluster of genes found in all mammals
- Its products play role in discriminating self/non-self
- Participant in both humoral and cell-mediated immunity
- MHC Act As Antigen Presenting Structures

Location and Function of MHC

- Collection of genes within a long stretch of DNA on chromosome 6 in humans and chromosome 17 in mice
- MHC - Human Leukocyte Antigen (HLA)
- H-2 Complex (mice)
- MHC genes organized in regions encoding 3 classes of molecules

Genes Of MHC Organized In 3 Classes

Class I MHC genes

- Glycoproteins expressed on all nucleated cells
- Major function to present peptide Ags to TC

Class II MHC genes

- Glycoproteins expressed on M , B-cells, DCs
- Major function to present processed Ags peptides to TH

Class III MHC genes

- Class III molecules are not membrane proteins, are not related structurally to class I and class II molecules, and have no role in Ag presentation, although most play some role in immune responses.
- e.g., C2, C4a, C4b, factor B, 21-hydroxylase enzymes,TNFα, TNFβ, heat shock proteins (HSP)(include secreted proteins).

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

Figure 8-1
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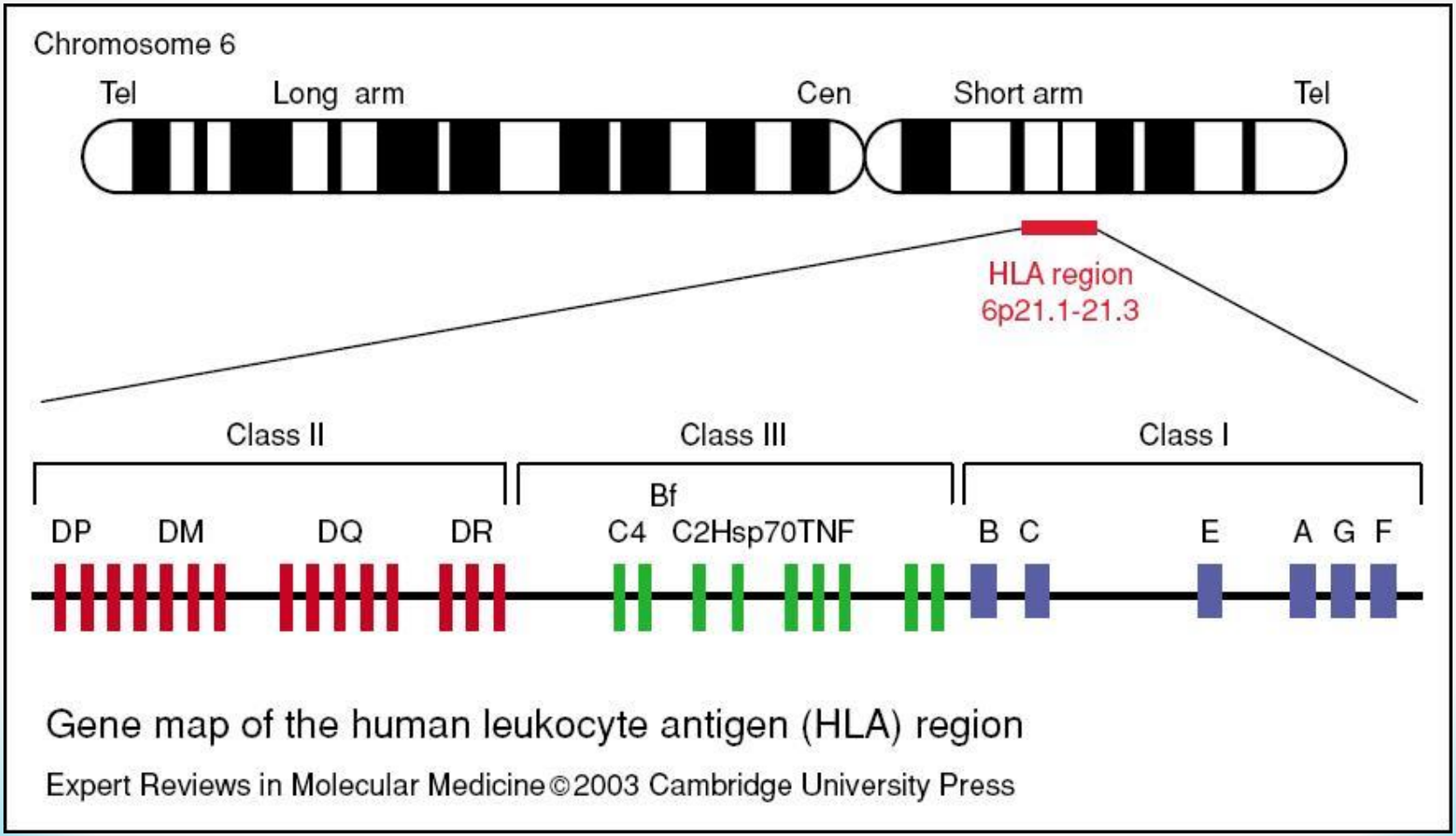
Chromosome 6: HLA region



Gene map of the human leukocyte antigen (HLA) region

Class I MHC Genes

- MHC Class 1 mediates immune responses against endogenous antigens, antigens that are already found in the cell.
- Usually, these cells that are expressing MHC class 1 are viral-infected or are tumor cells.
- MHC Class 1 presents peptides that are 8 – 10 amino acids in size, which will then be recognized by the cytotoxic T cells.
- MHC Class 1 is found on all nucleated cells.

Class I MHC Structure

- Contains large α chain associated with a smaller β_2-microglobulin molecule
- α chain is a polymorphic transmembrane glycoprotein (45 kDa)
- β_2- microglobulin molecule is an invariant protein (12kDa) encoded by a gene on a different chromosome
- Association of α chain with β_2 microglobulin is required for expression of Class I on cell membranes

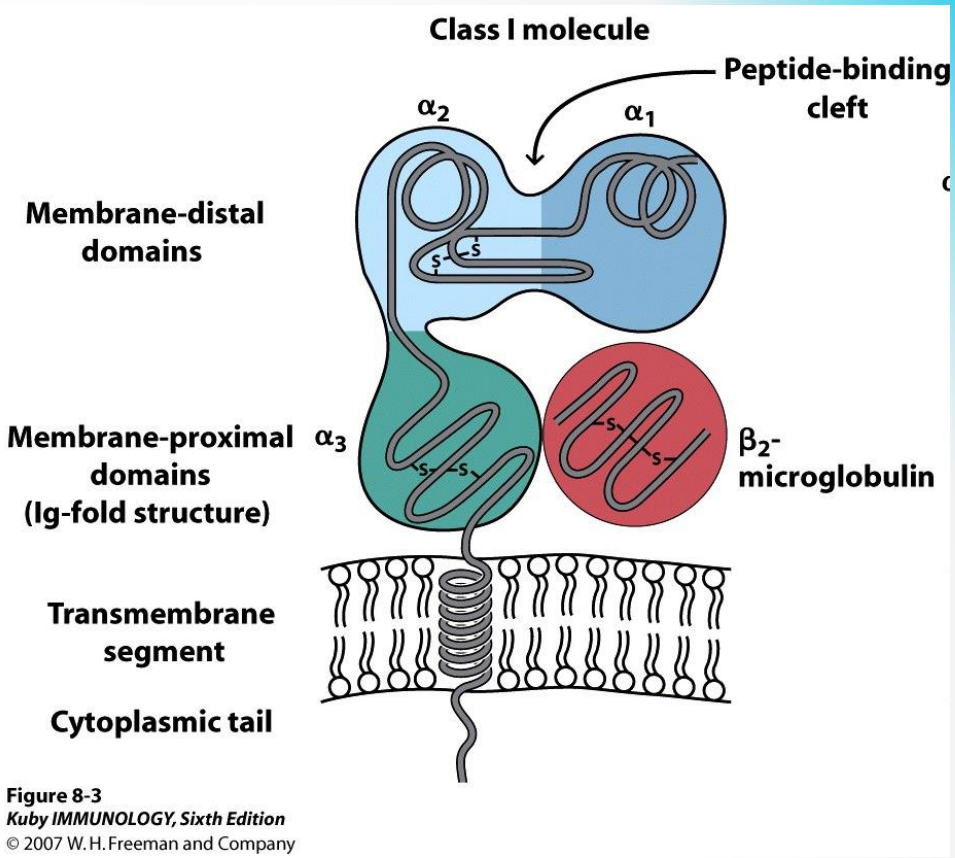


Figure 8-3
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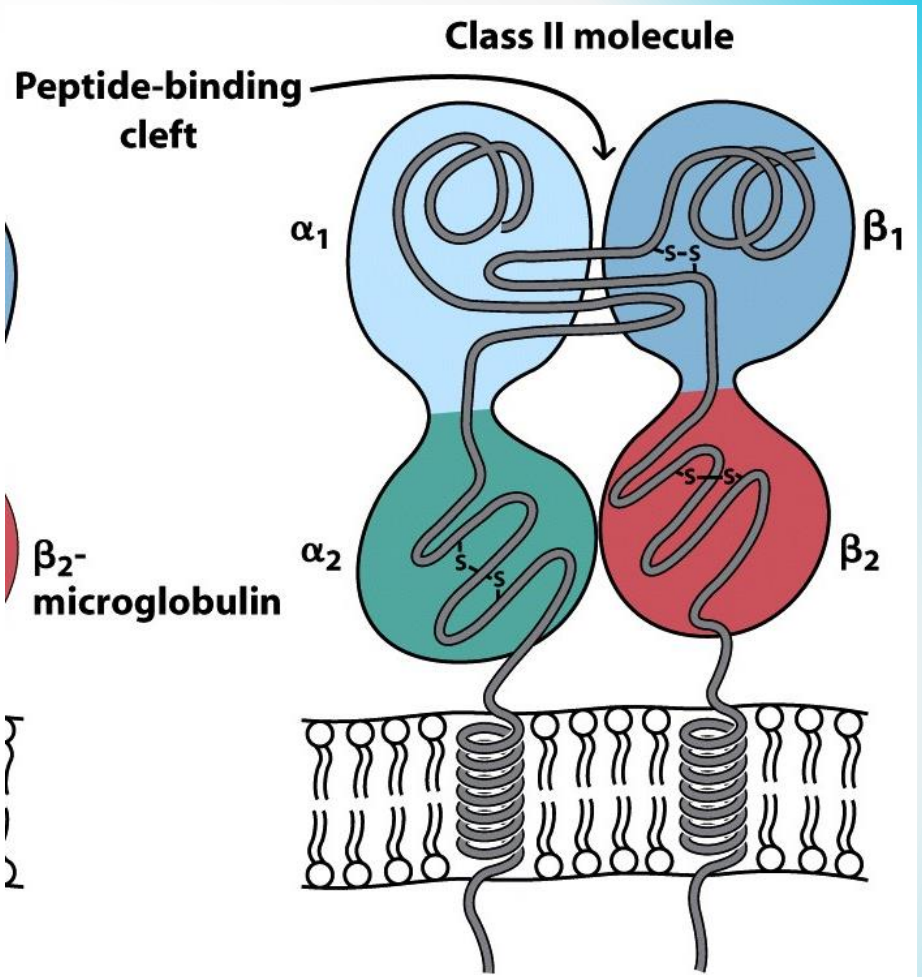
- α chain has 3 external domains
- Homology between α_3 & β_2 microglobulin & constant regions in immunoglobulins
- Peptide-binding cleft

Class II MHC Genes

- MHC class 2 mediates immune responses against exogenous antigens, antigens that are found outside of the cell, in the cytosol.
- MHC class 2 will bind with amino acid residues that are 13 – 18 in size and will be recognized by T helper cells.
- The MHC class 2 protein is found on cells like the B lymphocytes, macrophages, monocytes, dendritic cells, and endothelial cells.
- These cells are phagocytic and can engulf an extracellular antigen.



Contains 2 different polypeptide chains:
α chain (33 kDa) & a β chain (28 kDa)
Each chain has 2 external domains
Antigen binding cleft for processed antigens
αβ heterodimer "dimer of dimers"

Class III MHC Genes

- Generally encode secreted proteins associated with the immune process
- Reason for location within the MHC region is uncertain
- Several structurally & functionally diverse proteins encoded within the 3rd region of MHC
- Includes several complement components, tumor necrosis factors (α & β), 2 heat shock proteins
- Not membrane proteins and have no role in antigen presentation, although most play a role in immune response

MHC Haplotypes

- Haplotype- set of genes located on a single chromosome and the characteristics dependent on them
- An individual has 2 haplotypes of each set of genes (maternal/paternal).
- MHC genes expressed codominantly (both maternal and paternal products expressed in same cells

Peptide Interaction

TABLE 8-2 Peptide binding by class I and class II MHC molecules

	Class I molecules	Class II molecules
Peptide-binding domain	α1/α2	α1/β1
Nature of peptide-binding cleft	Closed at both ends	Open at both ends
General size of bound peptides	8–10 amino acids	13–18 amino acids
Peptide motifs involved in binding to MHC molecule	Anchor residues at both ends of peptide; generally hydrophobic carboxyl-terminal anchor	Anchor residues distributed along the length of the peptide
Nature of bound peptide	Extended structure in which both ends interact with MHC cleft but middle arches up away from MHC molecule	Extended structure that is held at a constant elevation above the floor of MHC cleft

Table 8-2
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Class I MHC peptide interaction

- Class I bind peptides & present these peptides to $CD8^+$ T-cells
- Each type of Class I (A,B,C in humans K,D,L in mice) bind unique set of peptides
- Single nucleated cell expresses 10^5 copies of each Class I molecule
- Many different peptides will be expressed simultaneously on the surface by Class I MHC
- Endogenous processing pathway

Class II MHC peptide interaction

- Class II MHC binds peptides and presents these peptides to $CD4^+$ T cells
- Can bind of variety of peptides
- Endocytic processing pathway

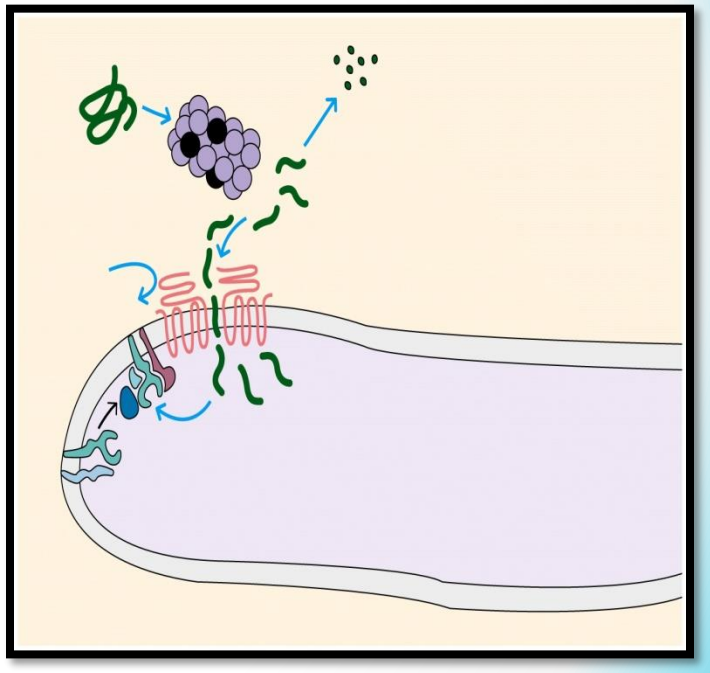
Polymorphism of Class I & II MHC

- Polymorphism - presence of multiple alleles at a given genetic locus within a species
- Diversity of MHC within a species results from polymorphism
- MHC expresses by an individual does not change over time but they may differ significantly from those expressed by another individual of the same species
- 10^{12} theoretical diversity of mice in each Class I & II MHC gene
- MHC also serve as antigens to let your immune system know what is self and what is non-self.
- The different allele combinations make up the identity of your MHC. Within each of these genes, there are many alleles.
- The main point is that there are lots and lots of alleles and thousands of combinations, which is why finding someone to whose HLA markers match up w/ another person is so difficult
- But it's not impossible, there are thousands of transplants every year.

Heat Shock Proteins

- Unusual group of highly conserved proteins that are produced by cells in response to various stresses including heat shock, nutrient deprivation, oxygen radicals, and viral infection
- Linked to certain autoimmune diseases

Antigen Processing & Presentation



- Formation of peptide-MHC complexes require that a protein antigen be degraded into peptides & displayed within the cleft of the MHC molecule on the cell membrane. The sequence of the above events is called *antigen processing.*
- The display of the transported peptide-MHC molecules on the cell membrane is called *antigen presentation*
- Class I MHC molecules bind peptides derived from endogenous antigens processed in the cytoplasm.
- Class II MHC molecules bind peptides derived from exogenous antigens that are internalized by phagocytosis or endocytosis & processed within the endocytic pathway.

Self-MHC Restriction of T cells

- Zinkernagel & Doherty demonstrated the self-MHC restriction of CD8+ T cells by immunizing mice with Lymphocyte choriomeningitis (LCM) virus.

- T_C cells only killed syngeneic virus-infected target cells, showing that T_C cell & the virus-infected target cell must share class I molecules encoded by K or D MHC regions.

Classic experiment of Zinkernagel and Doherty

- They demonstrate that antigen recognition by TC cells exhibits MHC restriction.

- H-2*k mice were primed with the lymphocytic choriomeningitis* (LCM) virus to induce cytotoxic T lymphocytes (CTLs) specific for the virus.

- Spleen cells from this LCM-primed mouse were then added to target cells of different H-2 haplotypes that were intracellularly labeled with 51Cr (black dots) and either infected or not with the LCM virus.

- CTL-mediated killing of the target cells, as measured by the release of 51Cr into the culture supernatant, occurred only if the target cells were infected with LCM and had the same MHC haplotype as the CTLs.

- CD4+ & CD8+ cells can only recognize antigen when presented on the membrane of a cell by a self-MHC molecule (*self-MHC restriction*).
- Rosenthal & Shevach showed that antigen –specific proliferation of TH cells only occurred in response to antigen presented by macrophage of the same MHC haplotype.
- These results indicate that the CD4+ TH cell can proliferate in response to antigen presented by macrophage that shared MHC alleles.
- - CD4 T cells are class II MHC restricted.

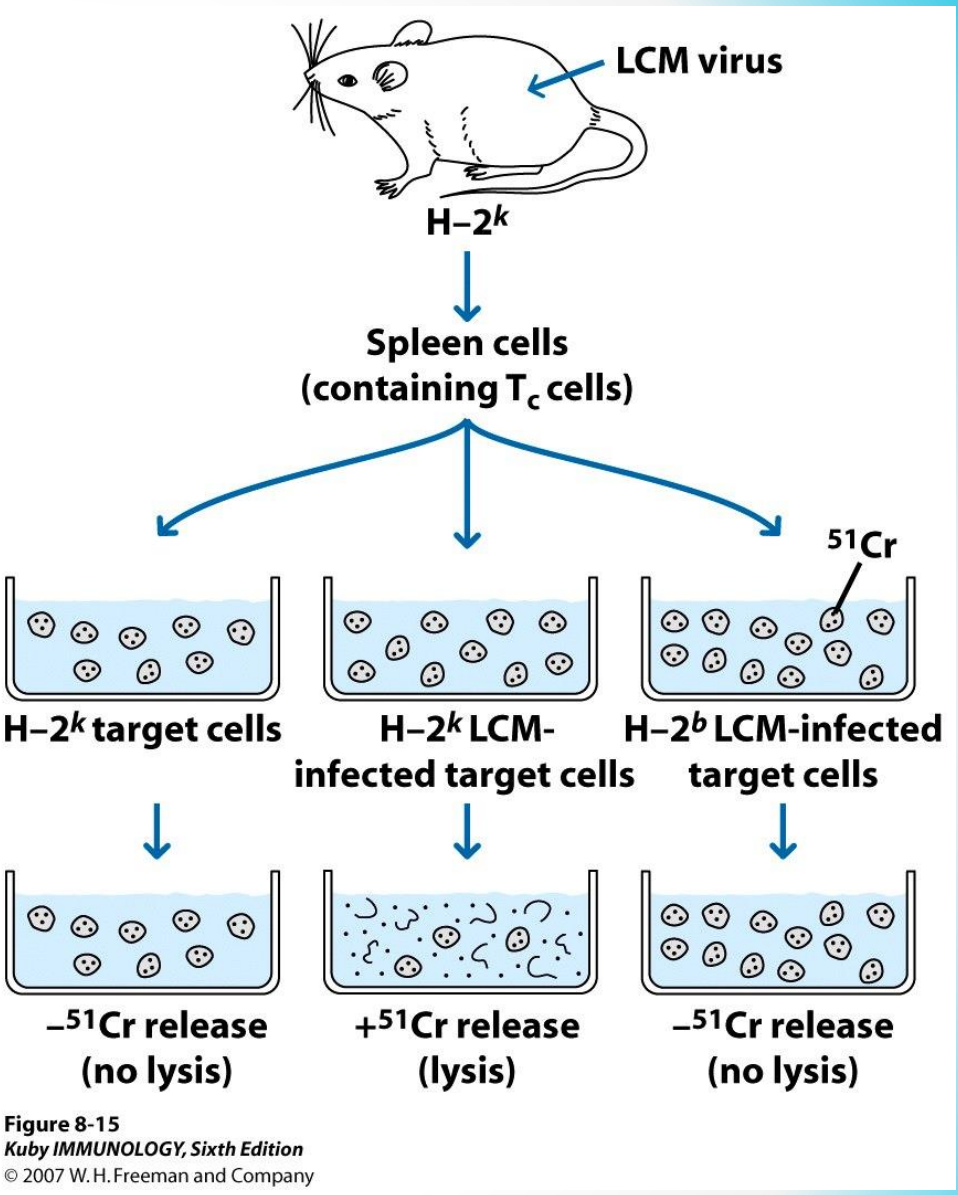


Figure 8-15
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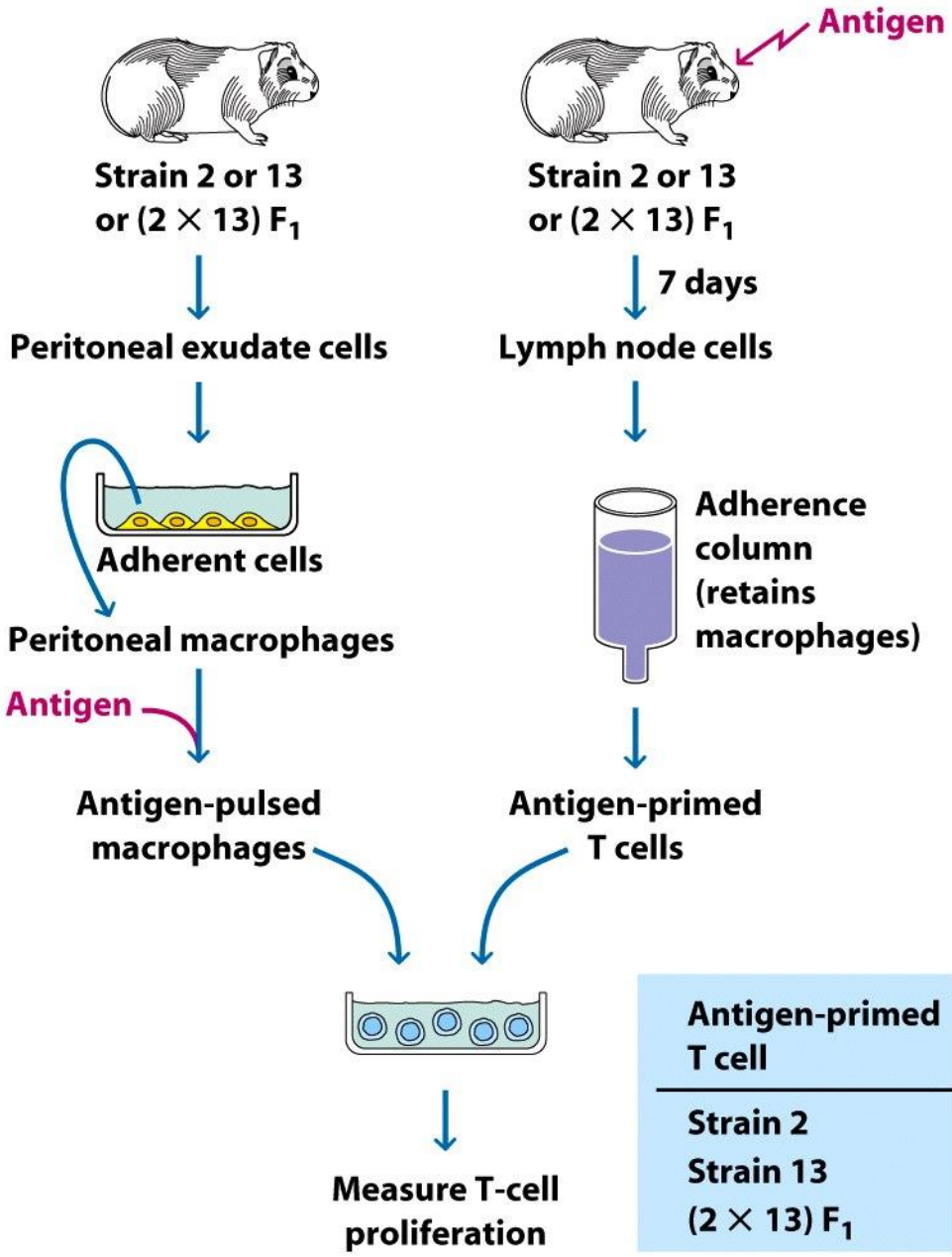

Experimental demonstration of self-MHC restriction of TH cells. Peritoneal exudate cells from strain 2, strain 13, or (2 13) F1 guinea pigs were incubated in plastic Petri dishes, allowing enrichment of macrophages, which are adherent cells. The peritoneal macrophages were then incubated with antigen. These "antigen-pulsed" macrophages were incubated in vitro with T cells from strain 2, strain 13, or (2 13) F1 guinea pigs, and the degree of T-cell proliferation was assessed. The results indicated that TH cells could proliferate only in response to antigen presented by macrophages that shared MHC alleles.

Antigen-primed T cell	Antigen-pulsed macrophages		
	Strain 2	Strain 13	(2 × 13) F_1
Strain 2	+	−	+
Strain 13	−	+	+
(2 × 13) F_1	+	+	+

Figure 8-14
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Antigen Presenting Cells

- Cells expressing class I or II MHC molecules can present peptides to T cells.
- By convention, cell that display peptides associated with class I MHC molecules to $CD8^+$ T cells are referred to as *target cells*.
- Those cells that display peptides associated with MHC class II molecules to T_H cells are called antigen presenting cells.

TABLE 8-3 Antigen-presenting cells

Professional antigen-presenting cells	Nonprofessional antigen-presenting cells	
Dendritic cells (several types)	Fibroblasts (skin)	Thymic epithelial cells
Macrophages	Glial cells (brain)	Thyroid epithelial cells
B cells	Pancreatic beta cells	Vascular endothelial cells

Table 8-3
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- Extracellular (exogenous) antigens are eliminated by secreted antibody whereas intracellular (endogenous) antigens are eliminated by CTLs.
- There are 2 different antigen-presenting pathway to mediate responses.

- Endocytic (Exogenous) pathway and Endogenous pathway

- Cytosolic pathway

Endocytic Pathway

- APCs can internalize antigen by phagocytosis &/or endocytosis.
- Macrophages do both; B cells use receptor-mediated endocytosis.
- After antigen is internalized, it is degraded into peptides.
- Internalized antigen takes 1-3 hours to traverse the endocytic pathway & appear on cell membrane in the form of peptide-class II MHC complexes.
- Internalized antigen moves from early to late endosomes & finally to lysosomes where they are hydrolyzed into oligopeptides of about 13-18 residues that bind to class II MHCs.

Endocytic Pathway *(cont.)*

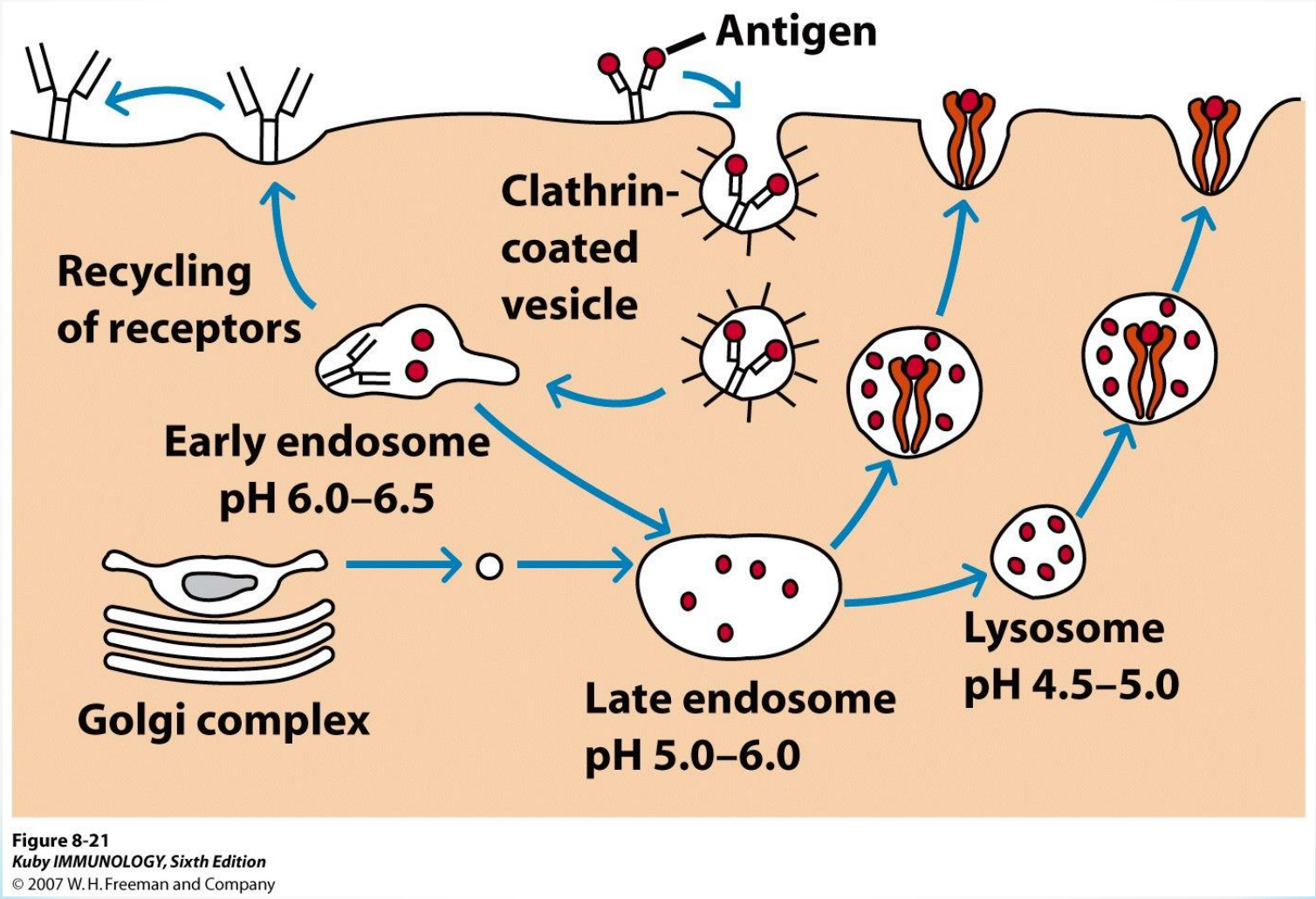

Figure 8-21
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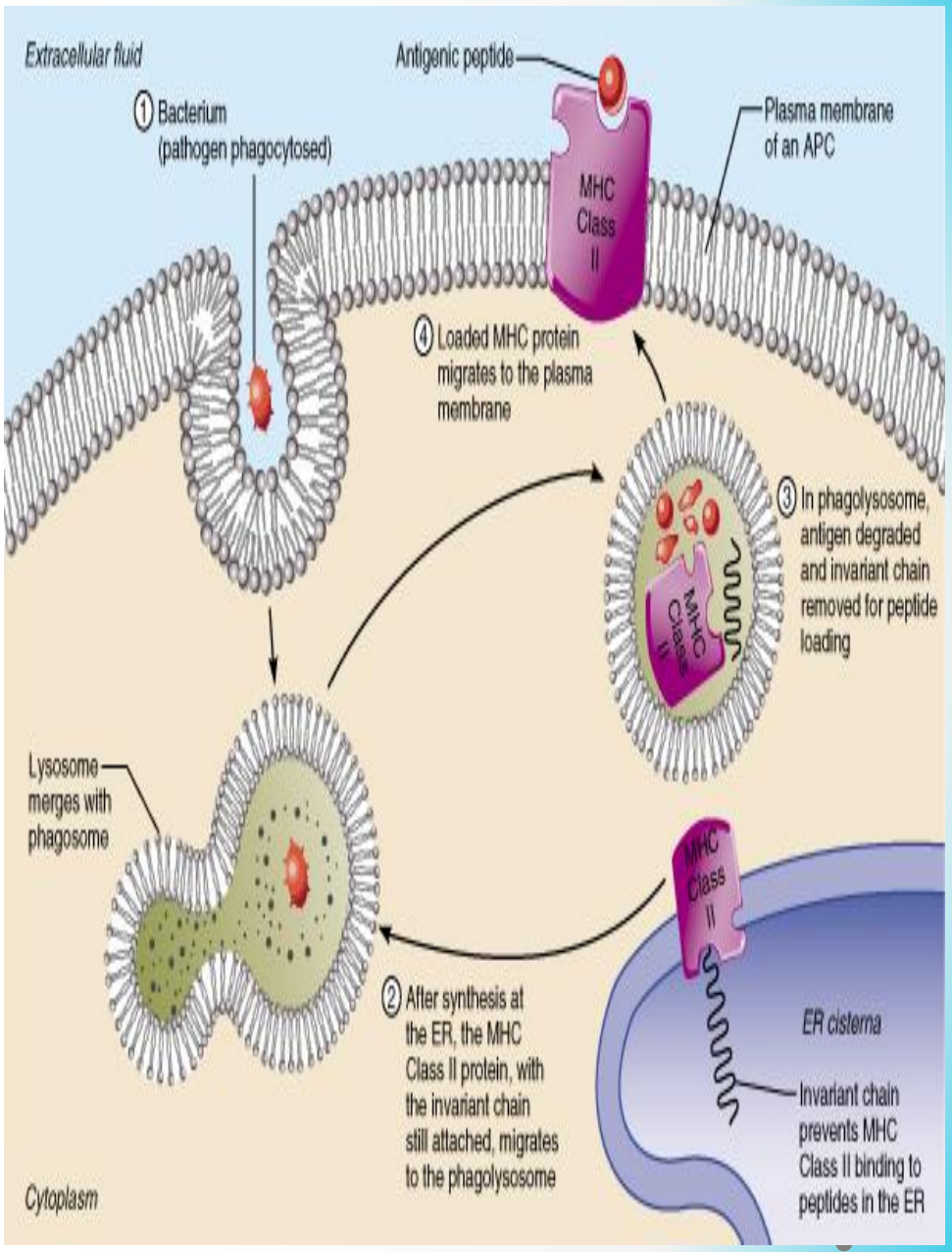
Exogenous Pathway

- The pathway begins by phagocytosis by the cell of a foreign agent, an organism, bacteria, etc…
- The antigen is now in a phagosome. A lysosome will fuse with the phagosome to become a phagolysosome.
- The antigen will be degraded into smaller peptides.
- With the help of sorting signals from the invariant chain (that's attached to the MHC class 2), the MHC class two will migrate to the phagolysosome, where it will bind to components that are 13 – 18 amino acids in size. Once bound, the MHC class 2 will migrate to the membrane to display the antigen.



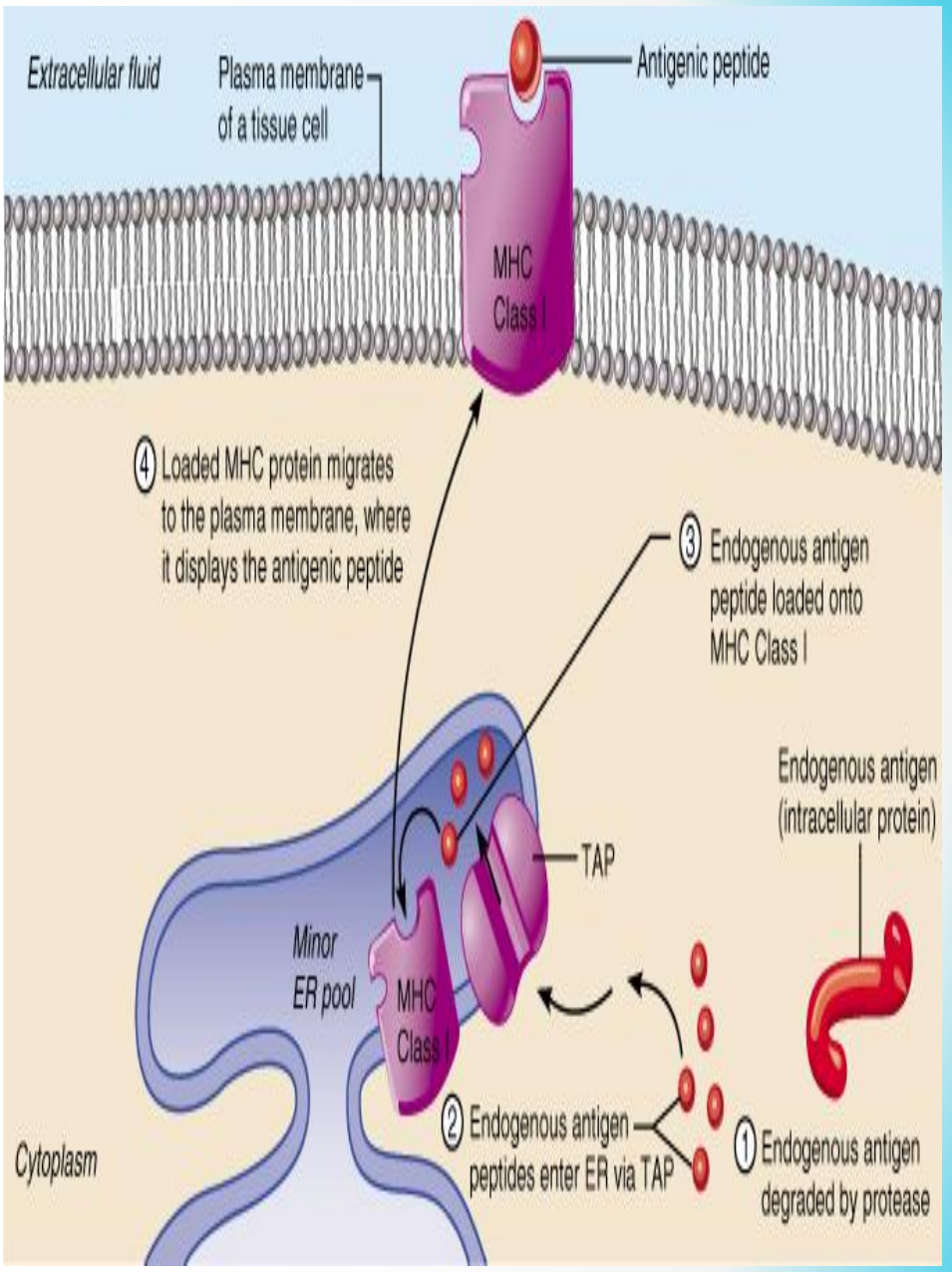
Endogenous Pathway

❖We start with an antigen that's already in the cell. It will be broken down into smaller peptides by a protease.

❖The peptides will be transported into the endoplasmic reticulum where MHC class 1 is located.

❖The 8 – 10 amino acid residues will bind with MHC class 1 and once that happens, the MHC class 1 and antigen will migrate to the cell surface, where it will present the antigen.

❖Cytotoxic T cells will recognize this complex and initiate the appropriate immune response to kill this cell.



Cytosolic Pathway

- Endogenous antigens are degraded into peptides that can be presented in class I MHC molecules to T_C cells involving similar mechanisms as of intracellular proteins.
- Ubiquitin → Ubiquitin-protein conj → Proteosome
- Subunits of large cytoplasmic proteolytic complex are called low-molecular mass polypeptides (LMP).

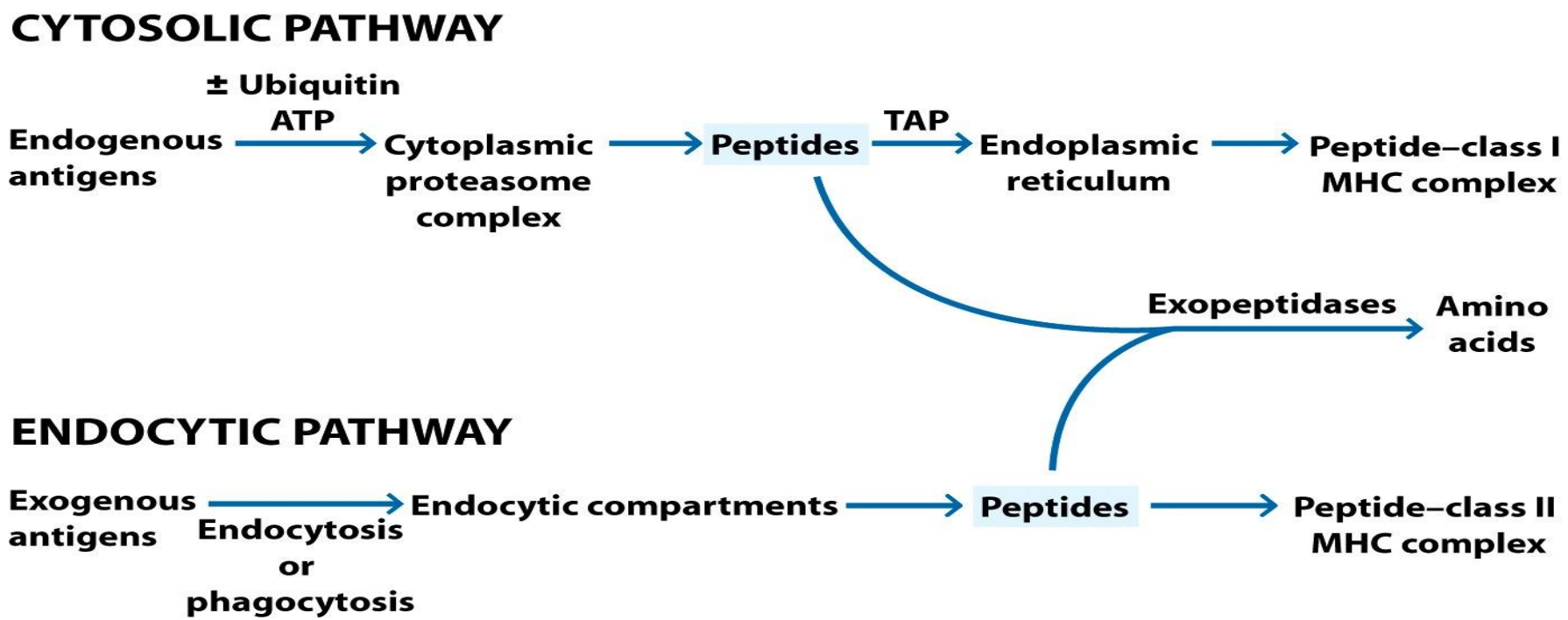


Figure 8-17
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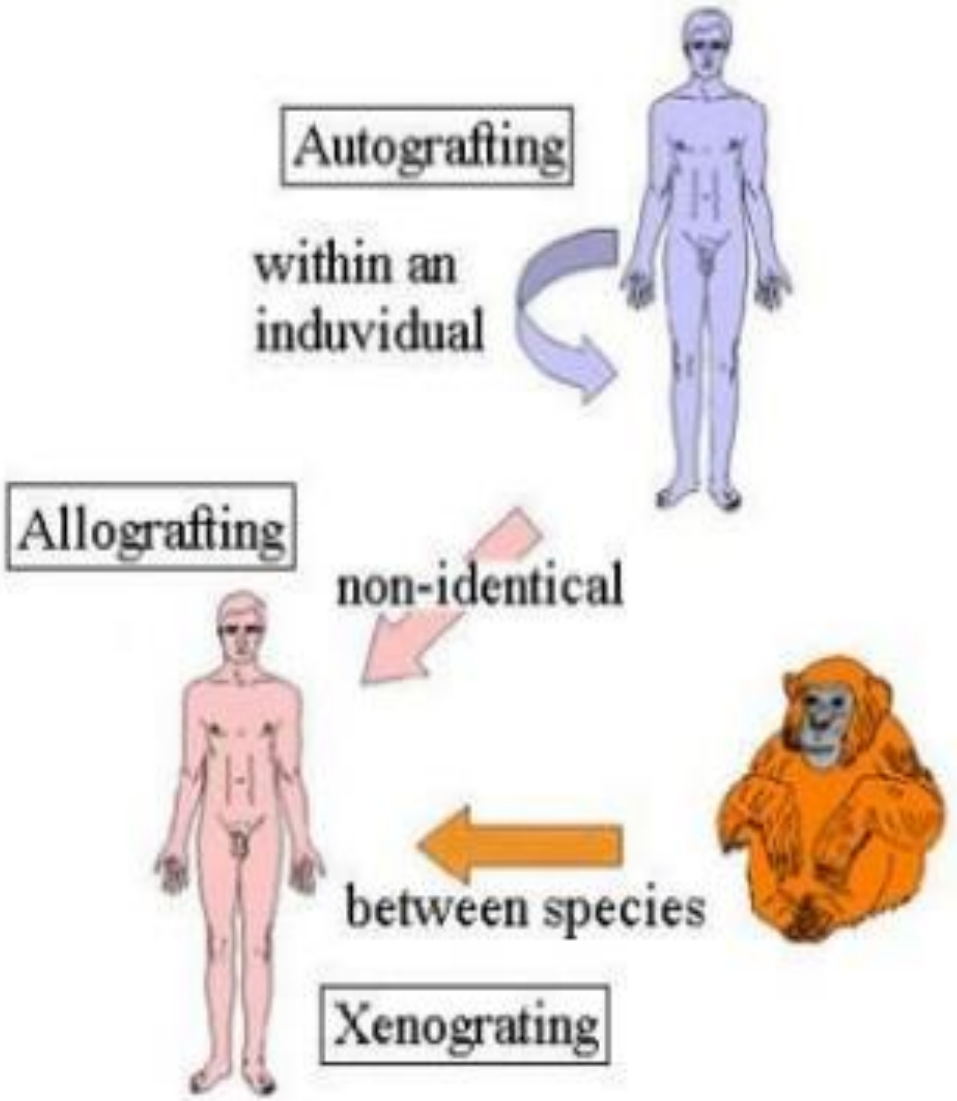
Tumor and Transplantation immunology

Transplantation Immunology

Transplantation Immunology

- Transplantation is a method of treating the patient with malfunctioned organ or tissue with the healthy one.
- The organ to be taken is called **graft** from a healthy individual referred as **donor** . The individual who receives the graft is called **recipient** .
- The transplantation is called **orthotropic** if the graft is used for an identical anatomical position and **heterotropic** if used in a different anatomical location.
- The blood from one individual can be transferred to another individual of same blood group and the process is called as **transfusion** .
- The method of transplantation can turn into **rejection** if the graft belongs to a genetically different individual.

- A graft transplanted from one part of body to other of a same individual is called **autologous graft** .
- A graft transplanted from one individual to a genetically identical individual is called **syngeneic graft**
- A graft transplanted from one individual to a genetically different individual is called **allogeneic graft (allograft)**
- A graft transplanted between individuals of two different species is called **xenogeneic graft (xenograft)** .
- The substances recognized as foreign by the host immune system in an allograft are called **alloantigens** and the lymphocytes and antibody against those are called **alloreactive** .
- Similarly, for xenograft the substances are called **xenoantigens** and counteracting immunity is called **xenoreactive** .

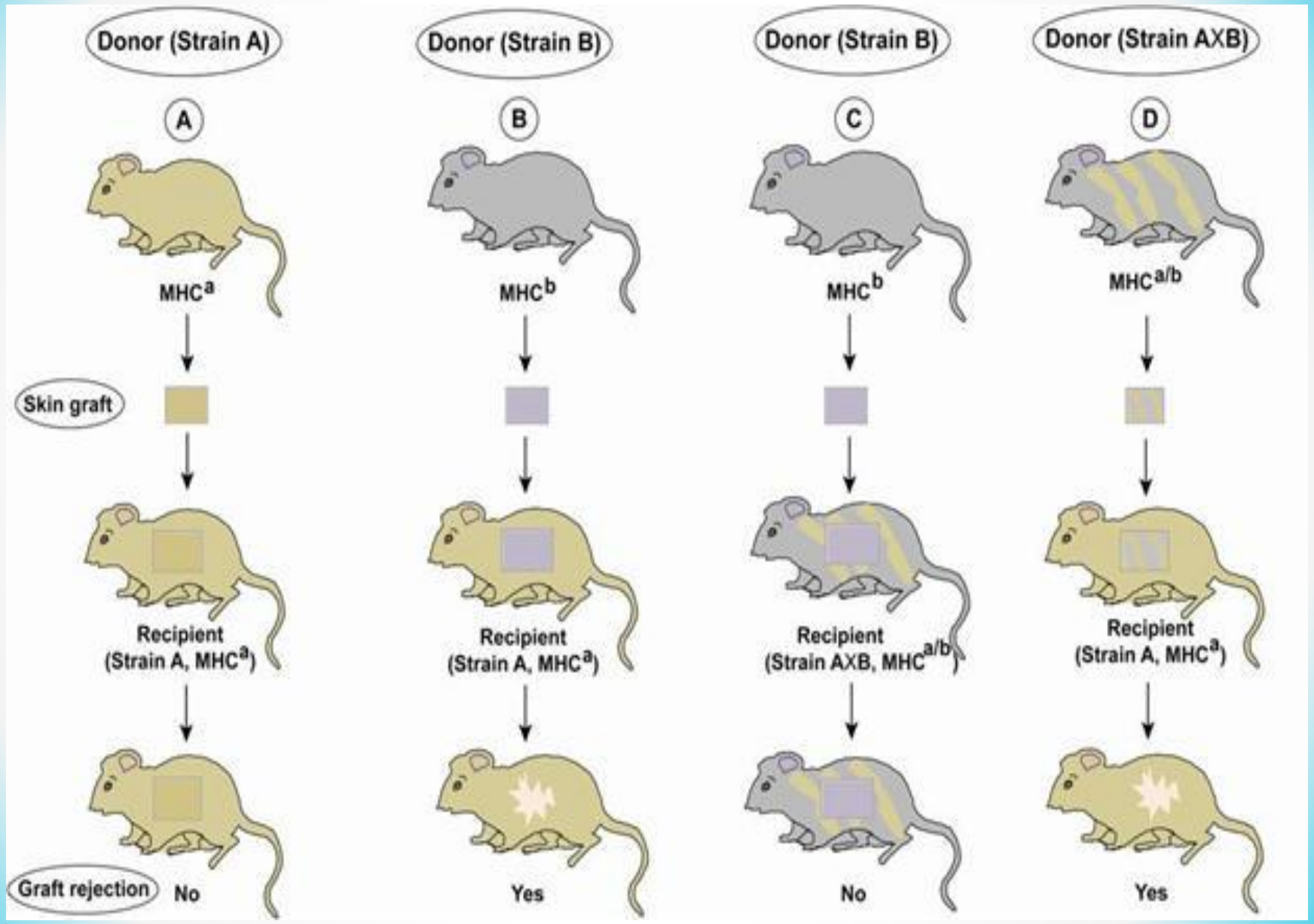


Immunity to allograft

Polymorphic genes called histocompatibility genes are responsible for the recognition of foreign transplant cells, and are very diverse among the individuals of same species. Some of the basic rules of transplantation are as follows

- Cells and organ transplanted between genetically identical individuals are not rejected.
- Cells and organ transplanted between two genetically non identical or different individuals are always rejected.
- The offspring of two different inbred animals usually do not reject the organ or tissue from either of the parents.
- The parents of an offspring belonging to two different inbred strains usually reject the graft taken from the offspring.

Genetics of graft rejection in mice:



- The molecules responsible for rejection of transplants are well known to be major histocompatibility complex (MHC).

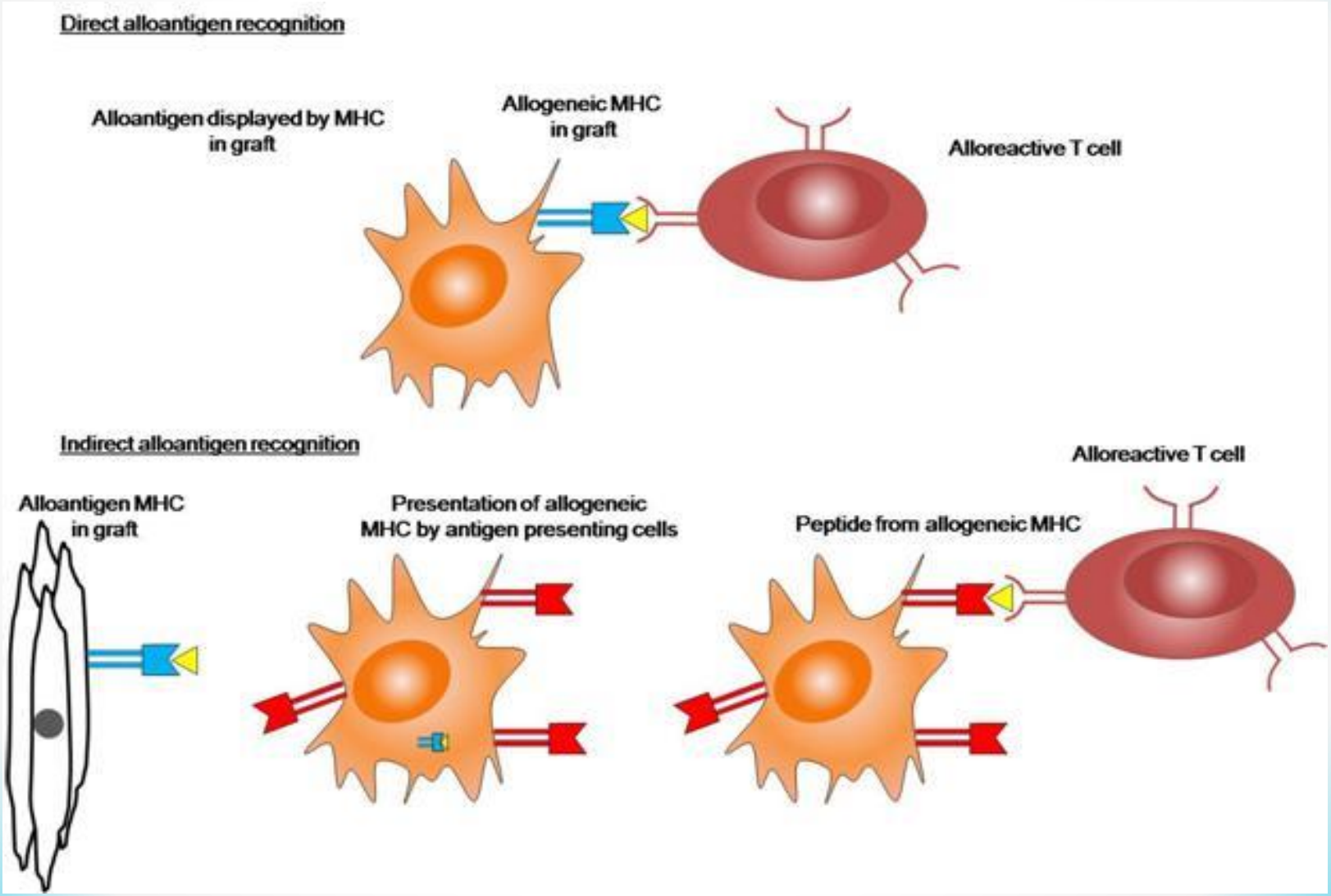
- The alloantigen from a foreign donor is presented to the T cell by MHC molecules.

The alloantigens are presented by typically two ways, direct and indirect.

In **direct presentation** , MHC molecules from the donor is directly presented to host T cells to elicit the cell mediated immune response without the involvement of host antigen presenting cells or MHC molecule.

In **indirect presentation** , the alloantigens are captured and processed by host antigen presenting cells and presented to T cells to elicit the immune response.

Direct and indirect recognition of allogeneic antigens:



Activation of alloreactive lymphocytes

- The alloantigens stimulate the B and T cell response similar to that of a protein antigen.
- Alloantigens can be recognized by T cells either by direct or indirect way and trigger a T cell immune response.
- Naïve lymphocyte migrates to lymph node after sensitization and differentiates into an effector cells that migrate back to the graft in order to induce rejection.
- Usually many of the T lymphocytes responding to alloantigens are memory T cells. In addition to alloantigen recognition by T lymphocyte, costimulatory molecules such as B7-1 also activate proliferation of lymphocytes.
- Similar to the processing of a protein antigen, the alloantigens that are processed by MHC class I can activate the CD8+ T cell response and those processed by MHC class II can activate CD4+ specific immune response.

Inhibition of allograft rejection

- The rejection of the allograft in a recipient having fully functional immune system is inevitable. It has been a challenging task to prevent the rejection of allograft in a recipient.
- An important area of research in the field of immunology is to avoid the rejection of an allograft and allow it to survive without any immune reactivity.

Many strategies have been adopted to avoid the rejection

I. Immunosuppressive drugs can be used to prevent graft rejection. **Cyclosporine** can inhibit the transcription of genes responsible for T cell activation and IL-2 secretion.**Rapamycin** inhibits the growth factor responsible for T cell activation.

II. Some antimetabolites that have the potential to kill the activating T lymphocyte can be used to prevent the alloreactive response.

III. **Inhibition of costimulatory** molecule is another strategy to prevent the rejection of the allograft.

.

IV. **Anti-inflammatory** drugs such as corticosteroids are frequently used to create an immunosuppressive condition in an individual and allow the survival of graft

Xenogeneic transplantation

- Transplantation of an organ from a different species has been a great interest for the scientist working on different human disease models.
- Transplantation of organs from pigs to human is an interesting outcome of the transplantation immunology.
- Pigs are preferred species for transplantation in human as compared to other species because of the anatomical compatibilities.
- However, the presence of natural antibodies such as IgM to the xenograft causes a hyperacute reaction in the recipients.
- The natural antibodies are mostly directed towards the carbohydrate present over the cell surface. Xenograft can also be rejected by T cell mediated immune responses similar to what is observed for the allograft.

Blood transfusion

- Blood transfusion is also a kind of transplantation in which blood is transferred from one individual to other having same blood group.

- The concept of blood grouping was put forth by **Karl Landsteiner** , who divided the blood into A, B, and O based on the presence of specific antigens. A, B, and O are the carbohydrate moiety present over the surface of blood cells.

- An individual having blood group A contains type “A” antigen and antibody against type B, so it will show rejection against blood group B. Same is true for blood group B antigen, which contains antibody against A. The blood group AB contains antigen against both A and B and do not produce antibody against any antigen hence the person of blood group AB can take blood from any individual hence called as **universal recipient** .

- The blood group O contains no antigen over its surface and produces antibody against both A and B hence can give the blood to any blood group individual and is called as **universal donor** .

- Individual having blood group AB can give blood to only AB individuals while blood group O individuals can only accept blood from an O group individual.

	Blood group A	Blood group B	Blood group AB	Blood group O
Antigens on RBC	A	B	Both A and B	None
Antibody Against	B	A	None	Both A and B
Accept blood from	A and O	B and O	A, B, AB and O	Only O
Donate blood to	A	B	AB	A, B, AB and O

Other blood group antigens

- The ABO blood group may be modified by the enzymes involved in the modification of the surface glycoproteins.
- The enzyme glycosyltransferase plays an important role in the terminal carbohydrate addition in the blood group antigens.
- The modification in which a different enzyme fucosyltransferase incorporates a fucosyl group at any other terminal position of the blood group antigen, results in the formation of **Lewis antigen** .

- Lewis antigen has a capacity to bind with E and P type selectin, making it a useful tool for immunologist.
- Another important blood group antigen is called Rh factor, named after Rhesus monkey from which it was first identified.
- The person can be Rh + or Rh - based on the presence or absence of Rh factor in the blood cells.
- The Rh - mother carrying an Rh + child can be sensitized by the Rh + factor circulating through the placenta in her blood.
- Since Rh factor will act as an antigen in mother's body and she will produce an IgG antibody against Rh factor.
- Any subsequent pregnancy can lead to abortion because of the destruction of the blood cells by antibodies against Rh factor; such condition is called **erythroblastosis fetalis** .

Graft versus host diseases

- Graft versus host disease (GVHD) occurs when a host is unable to reject the graft due to some form of immunosuppression.
- GVHD is usually caused by the antibody against MHC molecules of the host. GVHD is initiated by the grafted T cells that recognize the host alloantigens and mount an immune response in the form of effector T cell.
- The condition may be acute or chronic based on the severity of mounted immune response.
- Acute may be fatal while chronic GVHD leads to dysfunction of the affected organs.
- Natural killer cells, cytokines, and cytotoxic T lymphocytes are the major players of GVHD.

Tumor Immunology

Tumor Immunology

Immune surveillance

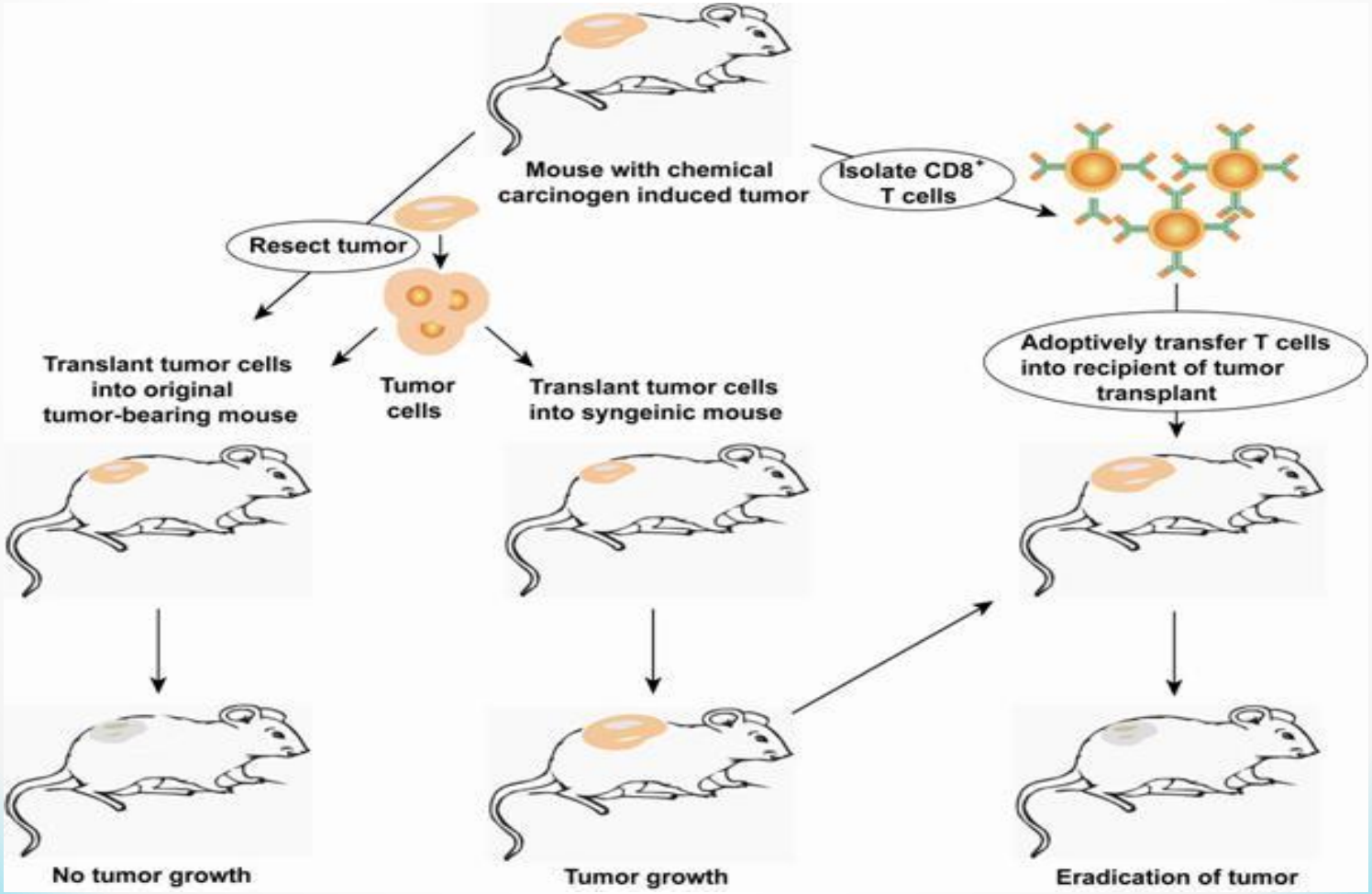
- The concept of immune surveillance was given by Macfarlane Burnet in 1950's.
- According to his definition of Immune surveillance physiologic function of the immune system is to identify cancerous or precancerous cells and remove them from the body before they cause any harm.

General features of tumor immunity

- One of the most important features is that tumors elicit specific adaptive immune responses. This can be proved due to the presence of T lymphocytes, natural killer cells and macrophages in the surroundings of the tumor cells.
- Tumor immunity is not sufficient to stop the growth of tumors. This study pattern undoubtedly raises questions about the concept of Immune surveillance.
- Outside source can be used to stimulate immune system to prevent and destroy the tumor cells.

- Mice treated surgically for chemical induced carcinogen gets immune to tumor growth following the injection of same tumor cells.

- Similarly, transfer of CD8+ cells to a recipient mice having tumor transplant rejects the tumor growth. However transplantation of same into a syngeneic mouse turned into a tumor mass.



Tumor antigens

- These are the antigens produced in tumor cells. Tumor antigens are classified based on how they express. Oncogenes and mutated tumor suppressor genes are identified as tumor antigens.

Tumor specific antigens – are the ones that do not express on normal cells but only on tumor cells.

Tumor associated antigens -are the ones that express on tumor as well as normal cells.

Antigens of oncogenic viruses - Oncogenic viruses such as Epstein – Barr virus, human papillomavirus and papovaviruses are associated with certain types of cancers in humans and animals. The end products of these oncogenic viruses act as tumor antigens and induce immunogenic response. This concept of immune response against virus induced cancers has paved way for the synthesis of vaccines against the tumor causing viruses.

Oncofoetal antigens - These are the proteins that are highly expressed in cancer cells as well as in foetus undergoing development but are absent in the adult cell.

Tissue specific differentiation antigens - These are tissue specific molecules expressed only on normal cells of origin and are not expressed on cells from other tissues.

Immune response to tumors

Tumor Immune response mostly occurs in two forms either by innate immune response or by adaptive immune response.

Innate immune response to tumors

Natural killer cells (NK cells)

- Around 15% of mammalian blood lymphocytes are composed of NK cells. NK cells can be activated by interferons from virus infected cells or by IL-12 from activated macrophages.

- NK cells are large, granular, and non-phagocytic cells that are derived from bone marrow.

- NK cells can kill certain tumor cell lines and are quite effective in eliminating the cells that diminish class I MHC expression.

- Studies also indicate that patients with deficiency of NK cells are more likely to suffer from EBV- associated lymphomas.

- NK cells express CD56 and CD16 antigen receptors over their surface. Activation of NK cells by antigen antibody reaction through CD16 kills the target cells.

Macrophages

- Macrophages can prevent the spread of cancer based on their activation state. Activated macrophages can kill transformed cells more efficiently than the normal cell.

- M1 cells especially treat the tumor cells like an infectious organism and produces cytokine tumor necrosis factor (TNF) to kill the tumor but M2 macrophages on the other hand are associated with tumor progression.

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Adaptive immune response to tumors

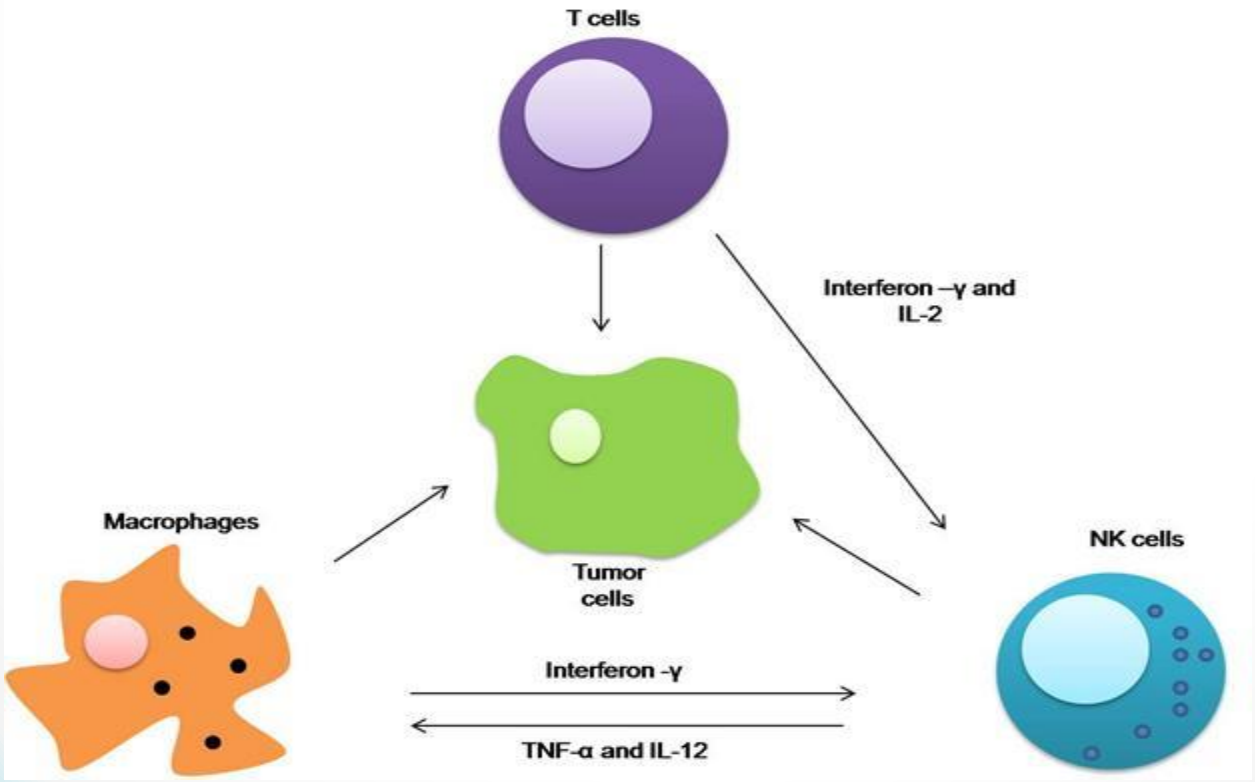
T-lymphocytes

- The basis of adaptive tumor immunity is to destroy tumor cells by CD8+ CTLs.
- Functioning of CD8+ cell requires cross presentation of the tumor antigen by the dendritic cells.
- Although CD8+ CTLs have a substantial role to play in killing the transformed clones but not much is known about the efficacy of CD4+ helper T –cells in tumor immunity

Antibodies

- These are known to kill tumors either by stimulating antibody-dependent cell mediated cytotoxicity or by the activation of complement system.

- Even though there is some immune response by antibodies in which NK cells mediate the destruction of tumor cells but antibody response towards tumors is not quite effective in most of the tumor cases.



Immune response to tumor

Evasion of immune response by tumors

Immune evasion by tumors can be divided into intrinsic or extrinsic mechanisms based on how these mechanisms are mediated.

Intrinsic mechanism of immune evasion by tumor cells

- Tumor cells are highly prone to mutation due to increased mitotic rate and hence the antigen expression may change at times and within a particular period tumor cells may lack or be deficit of the antigens that generate immune response.
- Immune system may not have access to the tumor cells because of antigen masking effect of**glycocalyx** molecules. Glycocalyx molecules help in hiding the tumor cells from the immune system by getting expressed in higher amounts in tumor cells.
- Tumor cells may prevent the immune response by associating with molecules that destroy the immune system.
- Some of the released products from the tumor cells may prevent the immune response. e.g TGF-β inhibits lymphocytes and macrophages.
- Tumor cells do not express class II MHC molecules so they may not elicit effective T cell immune response.

Extrinsic cellular suppression of anti-tumor immunity

- M2 macrophages are associated with progression of tumor growth and thus these macrophages may suppress the T- cell response to the tumor cells.
- T- Cell immunity can be lowered by the presence of regulatory T cells.
- Myeloid – derived suppressor cells (MDSCs) are detrimental to T cell response and may recruit regulatory cells to suppress the immune response.

Immunotherapy for tumors

Immunotherapy has a potential role in transformed cells because it is less harmful than other known treatments for cancer (chemotherapy, radiotherapy and surgery). Some of the roles that immunotherapy can play are mentioned below

- Treatment of patient with cytokines and costimulators may help to increase the immunity against tumor.
- Tumor antigens can be used as a vaccine for the infected individuals.
- Tumor immunity can be augmented by blocking the inhibitory pathways.
- Stimulation of immune response can be done by local administration of polyclonal activators of lymphocytes.
- Another way of inducing immune response is to transfer antibodies and other immune effectors passively.

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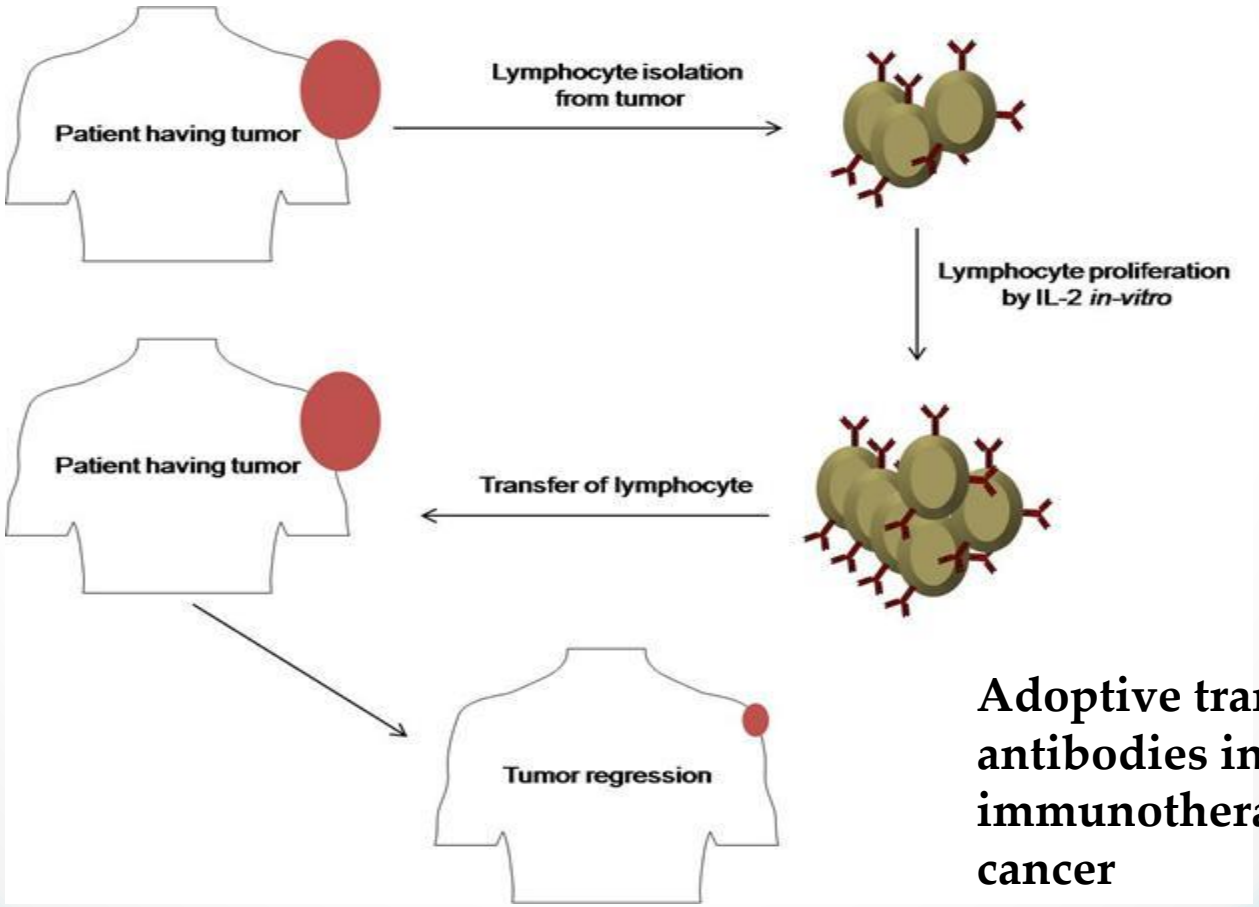
- Adoptive cellular immunotherapy can be approached which involves transfer of cultured immune cells in the host body.

- In some patients transfer of hematopoietic stem cell transplants combined with alloreactive T cells help in elimination of tumor.

- Monoclonal antibodies which are tumor specific may prove useful in some cases



Adoptive transfer of antibodies in immunotherapy for cancer

Immunotherapy for the treatment of cancer.

Cancer immunotherapy

- Cancer is the uncontrolled proliferation abnormal cells in the body

- There are five main categories of cancer:

    1. Carcinomas begin in the skin or tissues that line the internal organs.
    2. Sarcomas develop in the bone, cartilage, fat, muscle or other connective tissues.
    3. Leukemia begins in the blood and bone marrow.
    4. Lymphomas start in the immune system.
    5. Central nervous system cancers develop in the brain and spinal cord.

- Immunotherapy is also sometimes called biologic therapy or biotherapy.

- It is treatment that uses certain parts of the immune system to fight diseases such as cancer. It Stimulating your own immune system

- Cancer immunotherapy is the use of the immune system to reject cancer. The main premise is stimulating the patients immune system to attack the malignant tumor cells that are responsible for the disease

- In late 1800s Dr William Coley first noted that getting an infection after surgery seemed to help some cancer patients. he began treating cancer patients by infecting them with certain kinds of bacteria, which came to be known as Coley toxins.

- It represents the most promising new cancer treatment approach since the development of the first chemotherapies in the late 1940's.

- our immune system is a collection of organs, special cells, and substances that help protect us from infections and some other diseases.

- Immune cells and the substances travel through out our body to protect us from germs that cause infections.

- Immunotherapy use immune system components such as proteins called antibodies that are made in the lab. They boost the immune system once they are i the body. The antibodies themselves target certain proteins that help cancer cells grow. By binding to cancer-aiding proteins, the antibodies stop cancer cells from growing or make them die. These types of antibodies are also known as **TARGETED THERAPHY.**

Types of immunotherapy

- Monoclonal antibodies

  a) Naked mAbs

  b) Conjugated mAbs

    i. Radiolabelled
    ii. Chemolabeled
    iii. Immunotoxin

- Cancer vaccines

- Non-specific immune therapies

  a) Cytokines
  b) interleukin

MONOCLONAL ANTIBODIES:

These are INVITRO versions of immune system proteins. Antibodies can be very useful in treating cancer because they can be designed to attack a very specific part of a cancer cell.

CANCER VACCINES:

Vaccines are substances put into the body to start an immune response against certain diseases. We usually think of them as being given to healthy people to help prevent infections. But some vaccines can help prevent or treat cancer.

NON-SPECIFIC IMMUNTHERAPIES:

These treatments boost the immune system in a general way, but this can still help the immune system attack cancer cells.

MONOCLONAL ANTIBODIES

- One way the immune system attacks foreign substances in the body is by making large numbers of antibodies.
- An antibody is a protein that sticks to a specific protein called an antigen
- Antibodies circulate in the body until they find and attach to the antigen.
- Once attached, they can recruit other parts of the immune system to destroy the cells containing the antigen.
- the copies of that antibody synthesised in the lab. These are known as monoclonal antibodies (mAbs or moAbs).
- To make a monoclonal antibody, researchers first have to identify the right antigen to attack. For cancer, this is not always easy.
- Over the past couple of decades, the US Food and Drug Administration (FDA) has approved more than a dozen mAbs to treat certain cancers.

a. Naked monoclonal antibodies

- **Example :** alemtuzumab which is used to treat some patients with chronic lymphocytic leukemia (CLL).
- Alemtuzumab binds to the CD52 antigen, which is found on cells called lymphocytes (which include the leukemia cells).
- Once attached, the antibody attracts immune cells to destroy these cells.

b. Radiolabeled antibodies

It have small radioactive particles attached to them.

- **Eg**: Ibritumomab tiuxetan is an example of a radiolabeled mAb.
- This is an antibody against the CD20 antigen, which is found on lymphocytes called B cells.
- The antibody delivers radioactivity directly to cancerous B cells and can be used to treat some types of non-hodgkin lymphoma.

c. Chemolabeled antibodies

- These mAbs have powerful chemotherapy (or other) drugs attached to them.

- They are also known as antibody-drug conjugates (ADCs). (The drug is often too powerful to be used on its own – it would cause too many side effects if not attached to an antibody.)

CANCER VACCINES

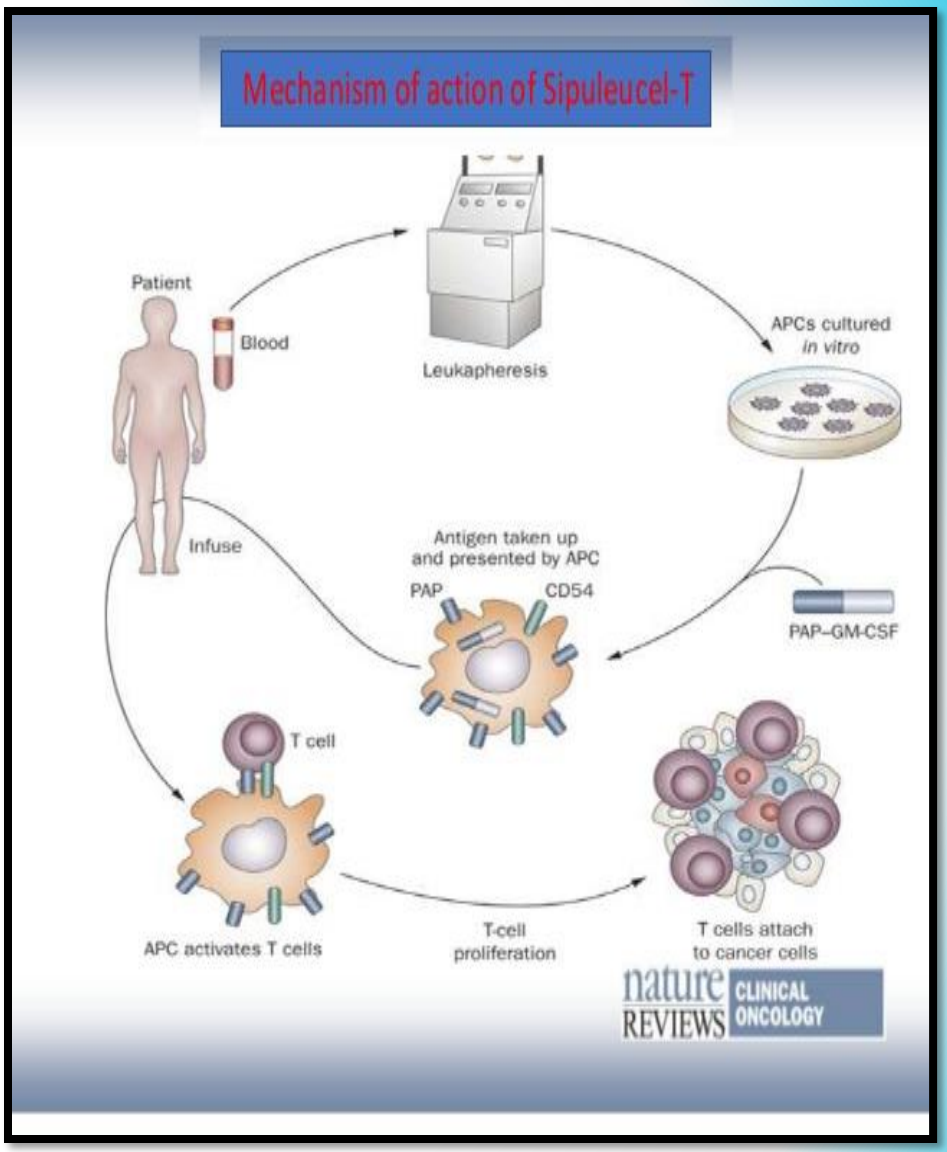
- vaccines use weakened or killed germs like viruses or bacteria to start an immune response in the body.

- Getting the immune system ready to defend against these germs helps keep people from getting infections.

- Some cancer treatment vaccines are made up of cancer cells, parts of cells, or pure antigens.

- Sometimes a patient's own immune cells are removed and exposed to these substances in the lab to create the vaccine.

- Once the vaccine is ready, it's injected into the body to increase the immune response against cancer cells.
- Cancer vaccines cause the immune system to attack cells with one or more specific antigens. Because the immune system has special cells for memory, it's hoped that the vaccine might continue to work long after it's given.
- Sipuleucel-T is the only vaccine approved so far by the US Food and Drug Administration (FDA) to treat cancer.
- It is used to treat advanced prostate cancer that is no longer being helped by hormone therapy.



NON-SPECIFIC CANCER IMMUNOTHERAPIES AND ADJUVANTS

- Non-specific immunotherapies don't target cancer cells specifically.

1. Cytokines

- Cytokines are chemicals made by some immune system cells.
- They are crucial in controlling the growth and activity of other immune system cells and blood cells in the body.
- Cytokines are injected, either under the skin, into a muscle, or into a vein.

2. Interleukins

- (IL-2) helps immune system cells grow and divide more quickly.
- A man-made version of IL-2 is approved to treat advanced kidney cancer and metastatic melanoma.

3. Interferons

- Interferons, first discovered in the late 1950s, help the body resist virus infections and cancers.

- The types of interferon (IFN) are named after the first 3 letters of the Greek alphabet: IFN-alfa, IFN-beta, and IFN-gamma.

- Only IFN-alfa is used to treat cancer. It boosts the ability of certain immune cells to attack cancer cells. It may also slow the growth of cancer cells directly, as well as the blood vessels that tumors need to grow.

The FDA has approved IFN-alfa for use against these cancers:

- Hairy cell leukemia
- Chronic myelogenous leukemia (CML)
- Follicular non-Hodgkin lymphoma
- Cutaneous (skin) T-cell lymphoma
- Kidney cancer
- Melanoma
- Kaposi sarcoma