MHC complex

Introduction

- Major Histocompactibility complex (MHC) is set of surface proteins located on the cell membrane of nucleated cells.
- It plays more important work to indentify the antigen between self and non self body, intracellular recognization and responsible for antigen presentation.
- Histo refers to tissues. Compatibility refers to living together harmoniously.
- MHC molecules always recognize only T lymphocytes. The two types of MHC are worked in immunity. T helper (Th) cell recognized by MHC molecules II, and T cytotoxic (Tc) cells are recognized by MHC I molecules.

Definition

- *"Major Histocompactibility complex is membrane attached protein which work on recognization of antigen between self and non self body and antigen presentation".*

4

History

Peter Gorer (1930) found that four group of MI molecules he used the blood sample of mice to identified blood group antigen which designated by I to IV group MHC.

Georg Snell, Jean Dausset and **Bariy** received noble prize 1980 for their contribution to the discovery of MHC molecul

Classes of MHC Molecules

- The MHC molecules are classified in to four classes namely ;-

1. Class I MHC molecules
2. Class II MHC molecules
3. Class III MHC molecules
4. Class IV MHC molecules

Class I MHC Molecules

- Class I MHC(45 KD) molecule are a group of major histocompactibility antigen.
- They are present on the surface of all nucleated cells except nervous tissue and platelets.
- It present antigen to **Tc** cells.
- It bind with **CD-8** adhesion molecules of **Tc** cells.
- It brings about **cell mediated immune response**.

Structure of Class I MHC Molecule

- It consists two polypeptide chains namely **α chain and β2 – micro globulin.**
- α chain which is non covalently attached with β2 microglobuline . α chain contain a transmembrane glycoprotein which is encoded by A,B and C gene of grouped HLA.
- α chain is organized by three domains such as α 1, α 2 and α 3 each domain containing 90 amino acids sequences .
- β2 microglobuline is similar in size of α 3 and it dose not contain trans membrane proteins .
- When the antigen is internalized and processed inside by proteosome (Ubiquitin, cytosolic degradation), the peptides are produced .
- Peptide is further loaded on the groove of MHC I molecules from endoplasmic reticulum.

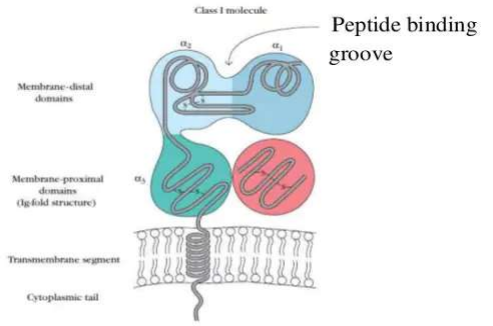


Fig:- Class I MHC antigen

Class II MHC Molecule

- Class II MHC molecule are present on the surface of antigen presenting cell and cell which engulfed the foreign antigen.
- It binds with the exogenous(endocytic degradation) antigens.
- It binds with CD4 adhesion molecules T_H cells.
- It also consist of two polypeptide chains namely α chain and β chain.
- Antigen is processed inside the **endosome** and peptide is further loaded on groove of MHC II molecules.

Structure of MHC II Molecule

- The class II MHC Molecule consists of two polypeptide chain namely α chain (33 kDa) and β (28kDa) chain.
- The both chain are attached noncovelantly.
- Each chain contains two units. The two units of α chain are called α1 and α2. The two domains of β chains are called β1 and β2.
- β2 and α2 are **transmembrane** domains anchoring the MHC to plasma membrane.
- The α1 and β1 domains jointly bear a **peptide binding groove.**

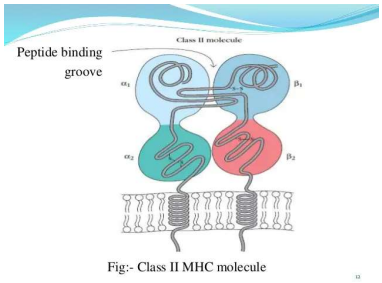


Fig:- Class II MHC molecule

Class III MHC molecule

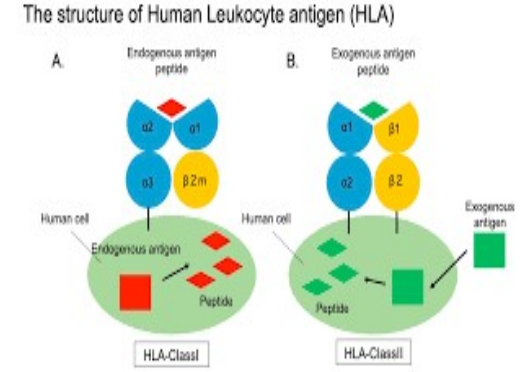
- The molecules include complements like C2 and C4 and B (factor B).

Class IV MHC molecule

- These molecule is present on T cells of leukemia(Tla) as well as on immature thymocytes .

HLA - Human Leukocyte Antigen

- **HLA** is the **human leukocyte antigen**.
- HLA is the MHC molecules present in human beings.
- HLA is a set of surface protein present on the surface of all nucleated cells. They are responsible for **graft rejection, adaptive immunity, defense against infection, some time it is expressed on cancer cell destruction, certain autoimmune diseases** and certain complements.
- MHC is the general term referring to the cell surface antigen of vertebrates.



H-2 Complex Of Mouse

The major histocompactibility complex (MHC) of mouse is called ***H-2* complex**.

H-2 complex is a **cluster of genes** responsible for the production of **antigens located of nucleated cells** and complement components.

This complex is located in the **short arm** of the chromosome number 17.

It consists of a **set of structural genes** .

The genes, that make up a given histocompactibility complex, are called **halotypes.**

Function of MHC Molecules

MHC molecules are loaded with a bit of sample peptide fragment derived from the **degradation of proteins** present inside the cell. This peptide is the **mirror image** of proteins present inside the cell.

MHC molecules contain **self** as well as **nonself (foreign)** antigen.

They bring about **defense against infections and diseases**.

They mediate certain **autoimmune diseases**.

They are responsible for **individual smell** of people.

Every vertebrate species studied to date possesses the tightly linked cluster of genes that constitute the MHC.

As we have discussed, MHC molecules have the important job of deciding which fragments of a foreign antigen will be "seen" by the host T cells.

In general terms, MHC molecules face a similar ligand binding challenge to that faced, collectively, by B-cell and T-cell receptors: they must be able to bind a wide variety of antigens, and they must do so with relatively strong affi nity.

However, these immunologically relevant molecules meet this challenge using very different strategies.

Although B- and T-cell receptor diversity is generated through genomic rearrangement and gene editing MHC molecules have opted for a combination of peptide binding promiscuity and the expression of several different MHC molecules on every cell

Using this clever combined strategy, the immune system has evolved a way of maximizing the chances that many different regions, or epitopes, of an antigen

studies of the MHC gene cluster originated when,

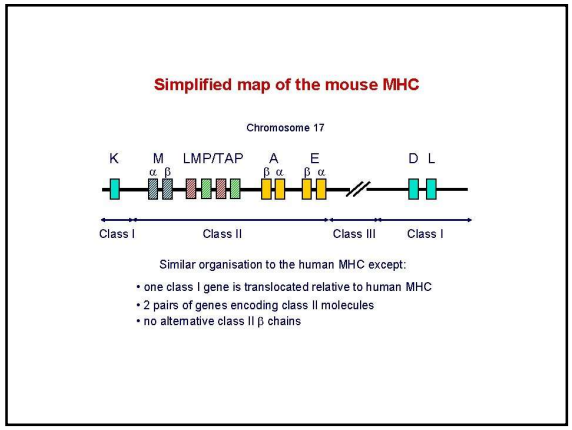
it was

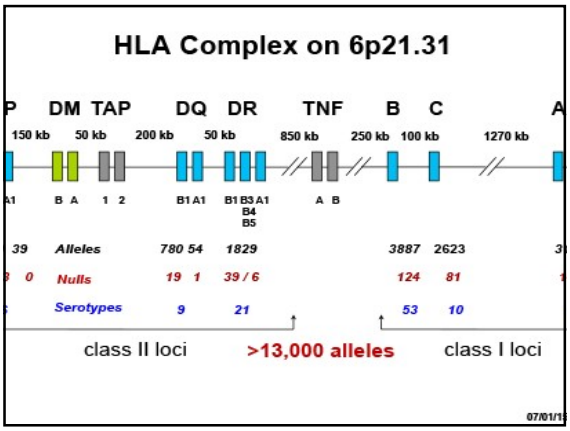
found that the rejection of foreign tissue transplanted between

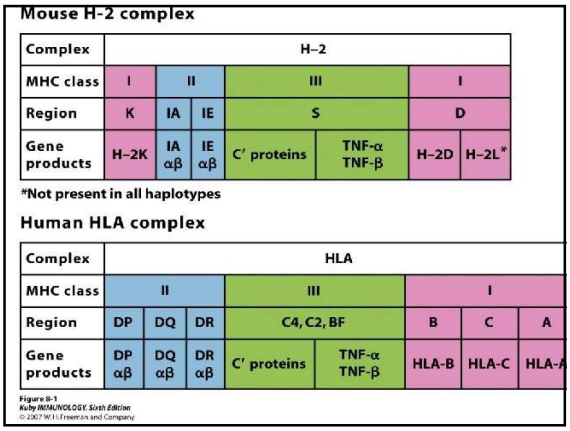
individuals in a species was the result of an immune response

mounted against cell surface molecules,

now called histocompatibility antigens.







- 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

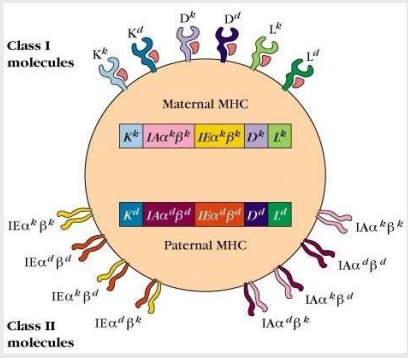
- Class I MHC genes encode glycoproteins expressed on the surface of nearly all nucleated cells; the major function of the class I gene products is presentation of endogenous peptide antigens to CD8 T cells.
- Class II MHC genes encode glycoproteins expressed predominantly on APCs (macrophages, dendritic 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.

- Separate exons encode each region of the class I and II proteins.
- Each of the mouse and human class I genes has a 5 leader exon encoding a short signal peptide followed by five or six exons encoding the chain of the class I molecule
- The signal peptide serves to facilitate insertion of the chain into the ER and is removed by proteolytic enzymes after translation is complete.
- The next three exons encode the extracellular 1, 2, and 3 domains, and the following downstream exon encodes the transmembrane (Tm) region.
- Finally, one or two 3-terminal exons encode the cytoplasmic domains (C).
- Like class I MHC genes, the class II genes are organized into a series of exons and introns mirroring the domain

Allelic Forms of MHC Genes Are Inherited in Linked Groups Called Haplotypes

- The genes that reside within the MHC region are highly polymorphic; that is, many alternative forms of each gene, or alleles, exist within the population.
- The individual genes of the MHC loci (class I, II, and III) lie so close together that their inheritance is linked.
- Crossover, or recombination between genes, is more likely when genes are far apart.
- For instance, the recombination frequency within the H-2 complex (i.e., the frequency of chromosome crossover events during meiosis,
- indicative of the distance between given genes) is only 0.5%.
- Thus, crossover occurs only once in every 200 meiotic cycles.
- For this reason, most individuals inherit all the alleles encoded by these genes as a set (known as linkage disequilibrium). This set of linked alleles is referred to as a haplotype. An individual inherits one haplotype from the mother and one haplotype from the father, or two sets of allele

And, the result is:



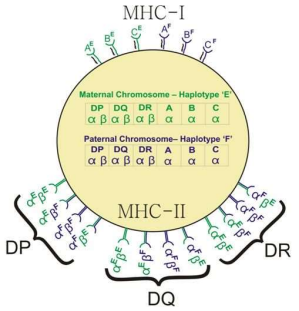
How many forms of HLA exist on cells?

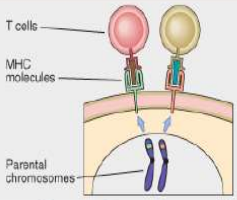
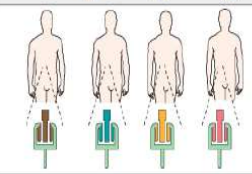
Genes display 'codominance'
-- up to 6 forms of MHC-I
-- 12+ forms of MHC-II

Peptides from different chromosomes can combine

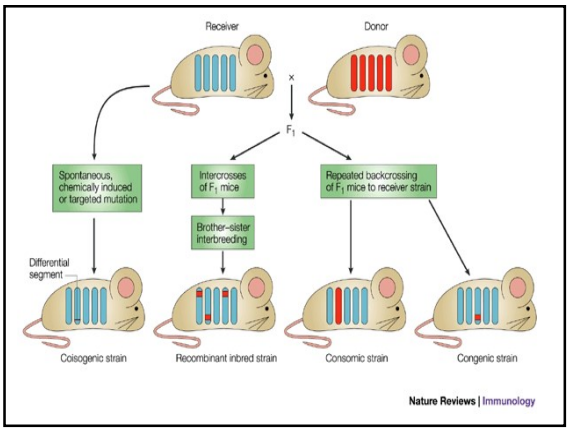
MHC proteins:
~ 10^5 copies / cell

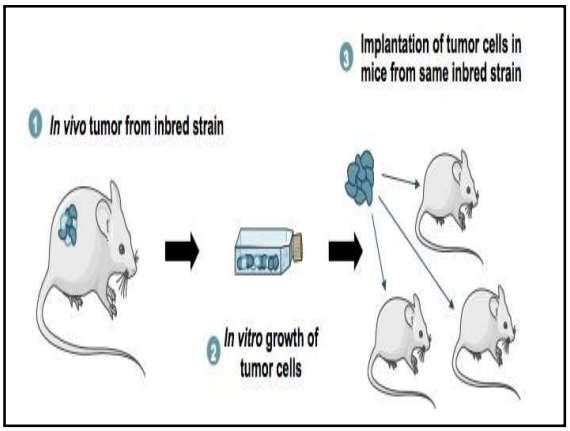
~10^{18} in species



Feature	Significance	
Co-dominant expression: Both parental alleles of each MHC gene are expressed	Increases number of different MHC molecules that can present peptides to T cells	
Polymorphic genes: Many different alleles are present in the population	Ensures that different individuals are able to present and respond to different microbial peptides	

- In outbred populations, such as humans, the offspring are generally heterozygous at the MHC locus, with different alleles contributed by each of the parents.
- If, however, mice are inbred, each H-2 locus becomes homozygous because the maternal and paternal haplotypes are identical, and all offspring begin to express identical MHC molecules.
- Certain mouse strains have been intentionally inbred in this manner and are employed as prototype strains.





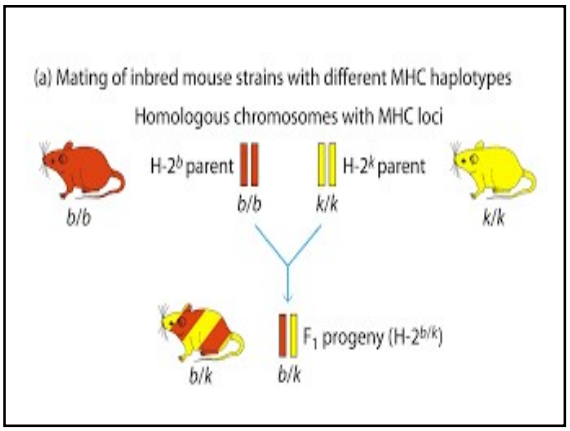
- The MHC haplotype expressed by each of these strains is designated by an arbitrary italic superscript (e.g., H-2a, H-2b).
- These designations refer to the entire set of inherited H-2 alleles within a strain without having to list the specific allele at each locus individually.
- Different inbred strains may share the same set of alleles, or MHC haplotype, with another strain (i.e., CBA, AKR, and C3H) but will differ in genes outside the H-2 complex.

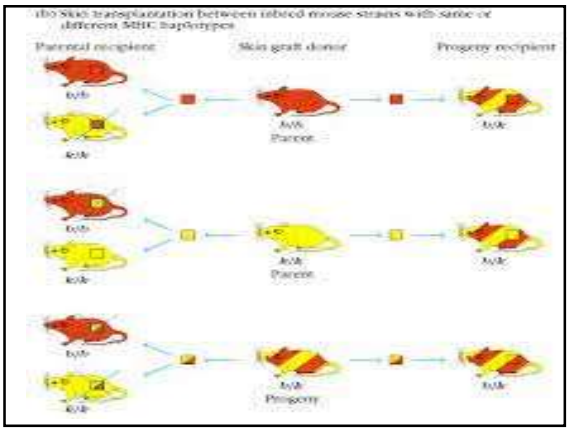
- Detailed analysis of the H-2 complex in mice has been made possible by the development of congenic H-2 strains that differ only at the MHC locus.
- Inbred mouse strains are said to be syngeneic, or identical at all genetic loci.
- Two strains are congenic if they are genetically identical except at a single genetic region.
- Any phenotypic differences that can be detected between congenic strains is therefore related to the genetic region that distinguishes the two strains.
- Congenic strains that are identical with each other except at the one point or loci

MHC Molecules Are Codominantly Expressed

- The genes within the MHC locus exhibit a codominant form of expression, meaning that both maternal and paternal gene products (from both haplotypes) are expressed at the same time and in the same cells.
- Therefore, if two mice from inbred strains possessing different MHC haplotypes are mated, the F1 generation inherits both parental haplotypes and will express all these MHC alleles.

- For example, if an H-2b strain is crossed with an H-2k strain, then the F1 generation inherits Nboth parental sets of alleles and is said to be H-2b/k .
- Because such an F1 generation expresses the MHC proteins of both parental strains on its cells, it is said to be histocompatible with both parental strains.
- This means offspring are able to accept graft s from either parental source, each of which expresses MHC alleles viewed as “self ” .
- However, neither of the inbred parental strains can accept a graft from its F1 offspring because half of the MHC molecules (those coming from the other parent) will be viewed as “nonself,” or foreign, and thus subject to recognition and rejection by the immune system.





- an outbred population such as humans, each individual is generally heterozygous at each locus.
- The human HLA complex is highly polymorphic, and multiple alleles of each class I and class II gene exist.
- However, as with mice, the human MHC genes are closely linked and usually inherited as a haplotype.
- When the father and mother have different haplotypes, as in the example ,
- there is a one-in-four chance that siblings will inherit the same paternal and maternal haplotypes and therefore will be histocompatible (i.e., genetically identical at their MHC loci) with each other; none of the off spring will be fully histocompatible with the parents.
- Although the rate of recombination by crossover is low within the HLA complex, it still contributes significantly to

- the diversity of the loci in human populations.
- Genetic recombination can generate new allelic combinations, or haplotypes , and the high number of intervening generations since the appearance of humans as a species has allowed extensive recombination.
- As a result of recombination and other mechanisms for generating mutations, it is rare for any two unrelated individuals to have identical sets of HLA genes.
- This makes transplantation between individuals who are not identical twins quite challenging! To address this, clinicians begin by looking for family members who will be at least partially histocompatible with the patient, or they rely on donor databases to look for an MHC match.
- Even with partial matches, physicians still need to administer heavy doses of immunosuppressive drugs to inhibit the strong rejection responses that typically follow tissue transplantation due to diff erences in the MHC proteins

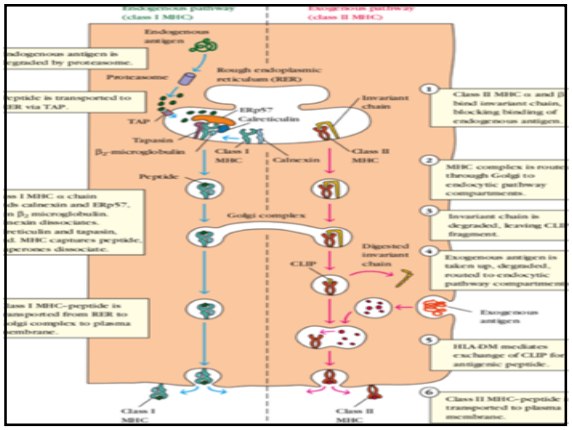
The Role of the MHC and Expression Patterns

- As we have just discussed, several genetic features help ensure a diversity of MHC molecules in outbred populations, including polymorphism, and codominant expression.
- All this attention paid to maximizing the number of different binding grooves suggests that variety within the MHC plays
- an important role in survival .
- In fact, in addition to fighting infection, MHC expression throughout the body plays a key role in maintaining homeostasis and health even when no foreign antigen is present.
- Although the presentation of MHC molecules complexed with foreign antigen to T cells garners much attention (and space in this book!), most MHC molecules spend their lives
- presenting other things, and oft en to other cells. Th ere are
- several reasons why an MHC molecule on the surface of a
- cell is important

- In general, these include the following:
- To display self class I to demonstrate that the cell is healthy
- To display foreign peptide in class I to show that the cell
- is infected and to engage with TC cells
- To display a self-peptide in class I and II to test developing T cells for autoreactivity (primary lymphoid organs)
- To display a self-peptide in class I and II to maintain tolerance to self-proteins (secondary lymphoid organs)
- To display a foreign peptide in class II to show the body is infected and activate TH cells

Evidence Suggests Different Antigen Processing and Presentation Pathways

- The immune system typically uses different pathways to eliminate intracellular and extracellular antigens.
- As a general rule, endogenous antigens (those generated within the cell) are processed in the cytosolic or endogenous pathway and presented on the membrane with class I MHC molecules.
- Exogenous antigens (those taken up from the extracellular environment by endocytosis) are typically processed in the exogenous pathway and presented on the membrane
- with class II MHC molecules .



The Endogenous Pathway of Antigen Processing and Presentation

- In eukaryotic cells, protein levels are carefully regulated.
- Every protein is subject to continuous turnover and is degraded at a rate that is generally expressed in terms of its half-life.
- Some proteins (e.g., transcription factors, cyclins, and key metabolic enzymes) have very short half-lives.
- Denatured, misfolded, or otherwise abnormal proteins also are degraded rapidly.
- Defective ribosomal products are polypeptides that are synthesized with imperfections and constitute a large part of the products that are rapidly degraded.

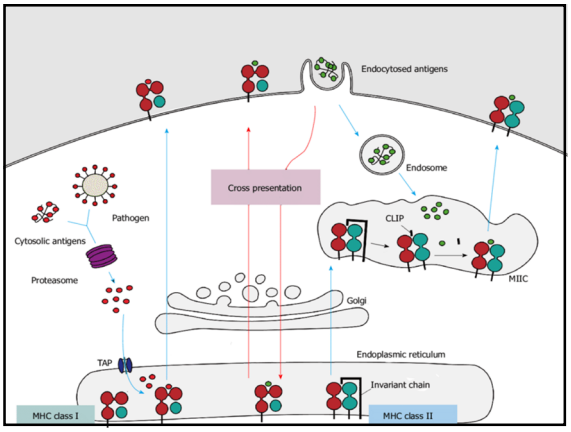
- The average half-life for cellular proteins is about 2 days, but many are degraded within 10 minutes.
- The consequence of steady turnover of both normal and defective proteins is a constant deluge of degradation products within a cell.
- Most will be degraded to their constituent amino acids and recycled, but some persist in the cytosol as peptides.
- The cell samples these peptides and presents some on the plasma membrane in association with class I MHC molecules, where cells of the immune system can sample these peptides to survey for foreign proteins.
- The pathway by which these endogenous peptides are generated for presentation with class I MHC molecules utilizes mechanisms similar to those involved in the normal turnover of intracellular proteins, but exactly how particular proteins are selected for degradation and peptide presentation still remains unclear

Peptides Are Generated by Protease Complexes Called Proteasomes

- Intracellular proteins are degraded into short peptides by a cytosolic proteolytic system present in all cells, called the Proteasome .
- The large (20S) proteasome is composed of 14 subunits arrayed in a barrel-like structure of symmetrical rings.
- Many proteins are targeted for proteolysis when a small protein called ubiquitin is attached to them.
- These ubiquitin-protein conjugates enter the proteasome complex, consisting of the 20S base and an attached 19S regulatory component, through a narrow channel at the 19S end.
- The proteasome complex cleaves peptide bonds in an ATP-dependent process.
- Degradation of ubiquitin-protein complexes is thought to occur within the central hollow of the proteasome.

- The immune system also utilizes this general pathway of the immune system also utilizes this general pathway of protein degradation to produce small peptides for presentation by class I MHC molecules.
- In addition to the standard 20S proteasomes resident in all cells, a distinct proteasome of the same size can be found in pAPCs and the cells of infected tissues.
- This distinct proteasome, called immunoproteasome, has some unique components that can be induced by exposure to interferon- or TNF-.
- LMP2 and LMP7, genes that are located within the class I region and are responsive to these cytokines, encode replacement catalytic protein subunits that convert

- standard proteasomes into immunoproteasomes increasing the production of peptides that bind efficiently to MHC class I proteins.
- The immunoproteasome turns over more rapidly than a standard proteasome, possibly because the increased level of protein degradation in its presence may have consequences beyond the targeting of infected cells.
- It is possible that in some cases autoimmunity results from increased processing of self-proteins in cells with high levels of immunoproteasomes.



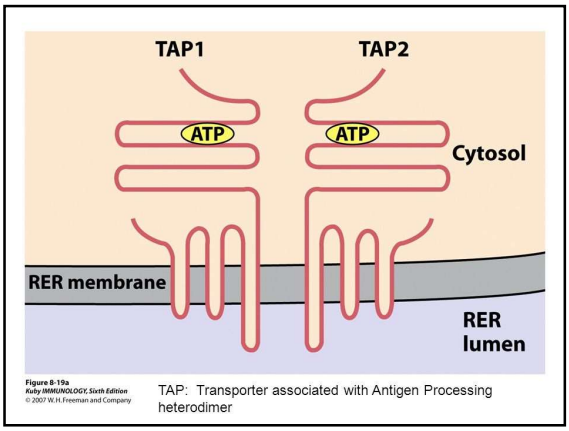
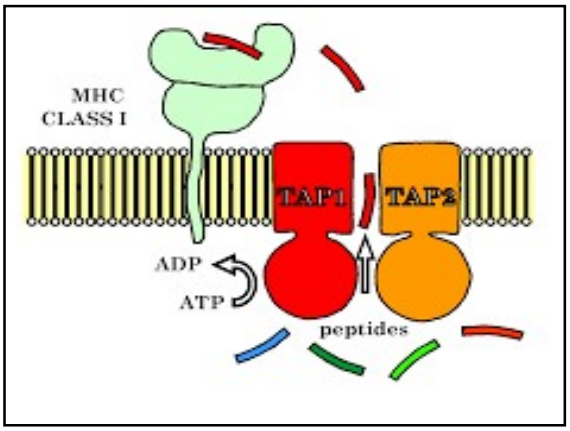


Figure 8-19a
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company

TAP: Transporter associated with Antigen Processing heterodimer



Peptides are transported from cytosol to Endoplasmic reticulum

- Insight into the cytosolic processing pathway came from studies of cell lines with defects in peptide presentation by class I MHC molecules.
- One such mutant cell line, called RMA-S, expresses about 5% of the normal levels of class I MHC molecules on its membrane.
- Although RMA-S cells synthesize normal levels of class I Alpha chain and Beta-2-microglobulin, few class I MHC complexes appear on the membrane.
- A clue to the mutation in the RMA-S cell line was the discovery by Townsend and his colleagues that "feeding" these cells peptides restored their level of membrane-associated class I MHC molecules to normal

These investigators suggested

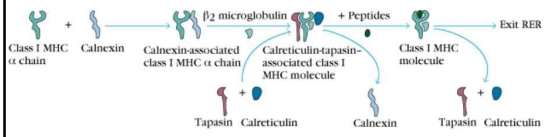
- that peptides might be required to stabilize the interaction between the class I Alpha chain and Beta-2-microglobulin.

- The ability to restore expression of class I MHC molecules on the membrane by feeding the cells predigested peptides suggested that the RMA-S cell line might have a defect in peptide transport.
- Subsequent experiments showed that the defect in the RMA-S cell line occurs in the protein that transports peptides from the cytoplasm into the RER, where class I molecules are synthesized.
- When RMA-S cells were transfected with a functional gene encoding the transporter protein, the cells began to express class I molecules on the membrane.
- The transporter protein, designated TAP (for transporter associated with antigen processing), is a membrane-spanning heterodimer consisting of two proteins: TAP1 and TAP2
- In addition to their multiple transmembrane

- segments, the TAP1 and TAP2 proteins each have a domain projecting into the lumen of the RER and an ATP-binding domain that projects into the cytosol.
- Both TAP1 and TAP2 belong to the family of ATP-binding cassette proteins found in the membranes of many cells, including bacteria.
- These proteins mediate ATP-dependent transport of amino acids, sugars, ions, and peptides.
- Peptides generated in the cytosol by the proteasome are
- translocated by TAP into the RER by a process that requires
- the hydrolysis of ATP .
- TAP has affinity for peptides containing 8 to 16 amino acids.
- Th e optimal peptide length for class I MHC binding is around 9 amino acids, and longer peptides are trimmed by enzymes present in the ER, such as ERAP (endoplasmic reticulum aminopeptidase).

- In addition, TAP appears to favor peptides with hydrophobic or basic carboxyl-terminal amino acids, the
- preferred anchor residues for class I MHC molecules.
- Thus, TAP is optimized to transport peptides that are most likely to interact with class I MHC molecules.
- The TAP1 and TAP2 genes map within the class II MHC region, adjacent to the LMP2 and LMP7 genes, and diff erent allelic forms of these genes exist within the population.
- TAP deficiencies can lead to a disease syndrome that has aspects of both immunodeficiency and autoimmunity.

3) Peptides Assemble with Class I MHC Aided by Chaperone Molecules



Assembly and stabilization of class I MHC molecules. Newly formed class I chains associate with calnexin, a molecular chaperone 伴护, in the RER membrane. Subsequent binding toβ 2-microglobulin releases calnexin and allows binding to the chaperonin calreticulin and to tapasin, which is associated with the peptide transporter TAP. This association promotes binding of an antigenic peptide, which stabilizes the class I molecule–peptide complex, allowing its release from the RER.

Chaperones Aid Peptide Assembly with MHC Class I Molecules

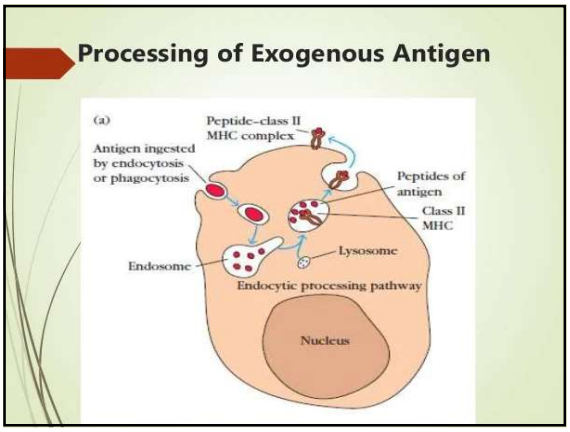
- Like other proteins destined for the plasma membrane, the Alpha- chain and Beta-2-microglobulin components of the class I MHC molecule are synthesized on ribosomes on the RER.
- Assembly of these components into a stable class I MHC molecular complex that can exit the RER requires the presence of a peptide in the binding groove of the class I molecule.
- The assembly process involves several steps and includes the participation of molecular chaperones that facilitate the folding of polypeptides.

- The first molecular chaperone involved in class I MHC assembly is calnexin, a resident membrane protein of the ER.
- ERp57, a protein with enzymatic activity, and calnexin associate with the free class I chain and promote its folding
- When Beta-2-microglobulin binds to the chain, calnexin is released and the class I molecule associates with the chaperone calreticulin and with tapasin.
- Tapasin (TAPassociated protein) brings the TAP transporter into proximity with the class I molecule and allows it to acquire an antigenic peptide.
- The TAP protein promotes peptide capture by the class I molecule before the peptides are exposed to the luminal environment of the RER.
- Exoproteases in the ER will act on peptides not associated with class I MHC molecules.
- One ER aminopeptidase, ERAP1, removes the amino-terminal residue from peptides to achieve optimum class I binding size .

- ERAP1 has little affinity for peptides shorter than eight amino acids in length.
- binding, the class I molecule displays increased stability and can dissociate from the complex with calreticulin, tapasin, and ERp57.
- The class I molecule can then exit from the RER and proceed to the cell surface via the Golgi complex.

The Exogenous Pathway of Antigen Processing and Presentation

- APCs can internalize particulate material by simple phagocytosis (also called "cell eating"), where material is engulfed by pseudopods of the cell membrane, or by receptor-mediated endocytosis, where the material first binds to specific surface receptors.
- Macrophages and dendritic cells internalize antigen by both processes.
- Most other APCs, whether professional or not, demonstrate little or no phagocytic activity and therefore typically internalize exogenous antigen only by endocytosis (either receptor-mediated endocytosis or by pinocytosis, "cell drinking").
- B cells, for example, internalize antigen very effectively by receptor-mediated endocytosis using their antigenspecifi c membrane immunoglobulin as the receptor



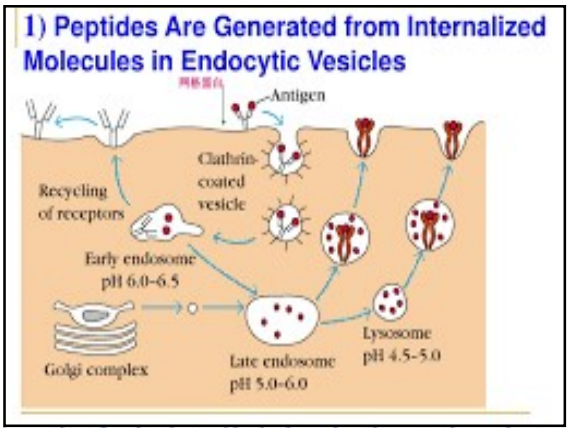
STEP-1

Peptides Are Generated from Internalized Antigens in Endocytic Vesicles

- Once an antigen is internalized, it is degraded into peptides within compartments of the endocytic processing pathway.
- internalized antigen takes 1 to 3 hours to traverse the endocytic pathway and appear at the cell surface in the form of class II MHC-peptide complexes.
- The endocytic antigen processing pathway appears to involve several increasingly acidic compartments, including early endosomes (pH 6.0–6.5); late endosomes, or endolysosomes (pH 4.5–5.0); and lysosomes (pH 4.5).
- Internalized antigen progresses through these compartments, encountering hydrolytic enzymes and a lower pH in each compartment .

- Antigen-presenting cells have a unique form of late endosome, the MHC class II-containing compartment (MIIC), in which final protein degradation and peptide loading into MHC class II proteins occurs.
- Within the compartments of the endocytic pathway, antigen is degraded into oligopeptides of about 13 to 18 residues that meet up with and bind to class II MHC molecules in late endosomes.
- Because the hydrolytic enzymes are optimally active under acidic conditions (low pH), antigen processing can be inhibited by chemical agents that increase the pH of the compartments (e.g., chloroquine) as well as by protease inhibitors (e.g., leupeptin).

- The mechanism by which internalized antigen moves from one endocytic compartment to the next has not been conclusively demonstrated.
- It has been suggested that early endosomes from the periphery move inward to become late endosomes and eventually lysosomes.



- transport vesicles may carry antigens from one compartment to the next.
- Eventually the endocytic compartments, or portions of them, return to the cell periphery, where they fuse with the plasma membrane. In this way, the surface receptors are recycled.

The Invariant Chain Guides Transport of Class II MHC Molecules to Endocytic Vesicles

- Since APCs express both class I and class II MHC molecules, some mechanism must exist to prevent class II MHC molecules from binding to the antigenic peptides destined for the class I molecules.
- When class II MHC molecules are synthesized within the RER, these class II chains associate with a protein called the invariant chain .
- This conserved, non-MHC encoded protein interacts with the class II peptide-binding groove preventing any endogenously derived peptides from binding while the class II molecule is within the RER .
- The invariant chain also appears to be involved in the folding of the class II and chains, their exit from the RER, and the subsequent routing of class II molecules to the endocytic processing pathway from the trans-Golgi network.

- The role of the invariant chain in the routing of class II molecules has been demonstrated in transfection experiments with cells that lack both the genes encoding class II MHC molecules and the invariant chain.
- Immunofluorescent labeling of these cells transfected only with
- class II MHC genes revealed that, in the absence of
- invariant chain, class II molecules remain primarily in

- the ER and do not transit past the cis-Golgi. However, in cells transfected with both the class II MHC genes and the Ii gene,
- the class II molecules were localized in the cytoplasmic vesicular structures of the endocytic pathway.
- The invariant chain contains sorting signals in its cytoplasmic tail that direct the transport of the class II MHC complex from the trans-Golgi network to the endocytic compartments.

Presentation of Nonpeptide Antigens

- To this point, the discussion of the presentation of antigens has been limited to protein antigens and their presentation by classical class I and II MHC molecules.
- that some nonprotein antigens are also recognized by T cells, and in the 1980s T-cell proliferation was detected in the presence of nonprotein antigens derived from infectious agents.

- Many reports now indicate that various types of T cells (expressing as well as T–cell receptors) can react against lipid antigens, such as mycolic acid, derived from well-known pathogens, such as Mycobacterium tuberculosis.
- These antigens are presented by members of the CD1 family of nonclassical class I molecules.

- Five human CD1 genes are known; all are encoded on a chromosome separate from the classical class I molecules and display very limited polymorphism.
- Much like classical MHC class I, CD1 proteins are formed by a transmembrane heavy chain, composed of three extracellular domains, which associates noncovalently with beta 2 microglobulin.
- In terms of traffi cking and expression profile, however, most CD1 molecules resemble MHC class II proteins, moving intracellularly to endosomal compartments, where they associate with exogenous antigen

- . Like MHC class II molecules, CD1 proteins are expressed by many immune cell types, including thymocytes, B cells, and DCs, although
- some members of the family have also been found on hepatocytes and epithelial cells.
- Many diff erent lipid or lipid-linked structures have been found to associate non-covalently with CD1 molecules. In
- general, most of these are glycolipid or lipoprotein antigens, where the lipid moiety fi ts into deep pockets within the CD1
- binding groove and the hydrophilic head group remains exposed, allowing recognition by T cells.
- Crystal structures have demonstrated that CD1 contains a binding groove that
- is both deeper and narrower than classical MHC molecules.
- These grooves are lined with nonpolar amino acids, which can easily accommodate lipid structures.

- The relatively nonspecifi c manner of antigen association with the CD1 binding groove, which relies primarily on many hydrophobic interactions, probably accounts for the diversity of self- and foreign antigens that can be presented by these nonclassical class I molecules.
- variety of T cells are known to bind these nonclassical MHC molecules.
- It is now hypothesized that short-chain self-lipids with relatively low affi nity are loaded onto CD1 molecules in the ER, shortly aft er translation, and allow proper CD1 protein folding.
- These self-antigen loaded CD1 molecules then travel to the cell surface, where in some cases exogenous lipids may be exchanged with these low-affi nity self-antigens.
- Like with MHC class II molecules, after endocytosis and movement tolower pH environments.