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THE HLA SYSTEM

First of Two Parts

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A MAN dies because his body has rejected a heart transplant; a woman is crippled by rheumatoid arthritis; a child goes into a coma that is brought on by cerebral malaria; another child dies of an infection because of an immunodeficiency; an elderly man has advanced hepatic cirrhosis caused by iron overload. These five clinical situations are as diverse as can be, yet all have one thing in common: the cause of all of them involves the human leukocyte antigen (HLA) system, the human version of the major histocompatibility complex (MHC). Malfunction of the HLA system, which is at the root of these and many other clinical disorders, has such wide-ranging effects not only because of the system's role in the adaptive immune response, but also because of its genetic complexity.

The HLA complex on chromosome 6 contains over 200 genes, more than 40 of which encode leukocyte antigens (Fig. 1).[1-3] The rest are an assortment of genes that are not evolutionarily related to the HLA genes themselves, although some are involved with them functionally.[4] Many genes within this complex have nothing to do with immunity. The HLA genes that are involved in the immune response fall into two classes, I and II, which are structurally and functionally different (Fig. 2). The class I genes code for the α polypeptide chain of the class I molecule; the β chain of the class I molecule is encoded by a gene on chromosome 15, the beta$_2$-microglobulin gene. The α chain has five domains: two peptide-binding domains (α1 and α2), one immunoglobulin-like domain (α3), the transmembrane region, and the cyto-

plasmic tail (Fig. 2). There are some 20 class I genes in the HLA region; three of these, HLA-A, B, and C, the so-called classic, or class Ia genes, are the main actors in the immunologic theater.

The class II genes code for the α and β polypeptide chains of the class II molecules (Fig. 2). The designation of their loci on chromosome 6 consists of three letters: the first (D) indicates the class, the second (M, O, P, Q, or R) the family, and the third (A or B) the chain (α or β, respectively). HLA-DRB, for example, stands for class II genes of the R family coding for the β chains. The individual genes of the HLA system are differentiated by Arabic numbers, and the notation for the numerous allelic variants of these genes is a number preceded by an asterisk. For example, HLA-DRB1*0401 stands for allelic variant 0401 of gene 1, which encodes the β chain of a class II molecule belonging to the R family. Each of the class II α and β chains has four domains: the peptide-binding domain (α1 or β1), the immunoglobulin-like domain (α2 or β2), the transmembrane region, and the cytoplasmic tail (Fig. 2).

Class I genes are expressed by most somatic cells, although the level of expression varies depending on the tissue.[1] By contrast, class II genes are normally expressed by a subgroup of immune cells that includes B cells, activated T cells, macrophages, dendritic cells, and thymic epithelial cells.[1] In the presence of interferon-γ, however, other types of cells can express class II HLA molecules. The function of both class I and class II molecules is the presentation of short, pathogen-derived peptides to T cells, a process that initiates the adaptive immune response. To understand this function, it is necessary to place it in the context of the cell's physiology, in particular the process of waste disposal.

ANTIGEN PROCESSING AND PRESENTATION

Cells are equipped with an enviably clean and efficient system of waste disposal and recycling. A special molecule, ubiquitin, marks worn-out proteins for dumping (Fig. 3A). These proteins unfold with the help of other specialized molecules, the chaperones, and the polypeptide chains are then fed into barrel-shaped structures, the proteasomes, which chop them up into short fragments.[5] The peptides emerging from the proteasome are either degraded into amino acids in the cytosol or transferred into the endoplasmic reticulum.

Extracellular proteins take a different route to degradation (Fig. 3B). They are herded into small bags that invaginate from the plasma membrane into the
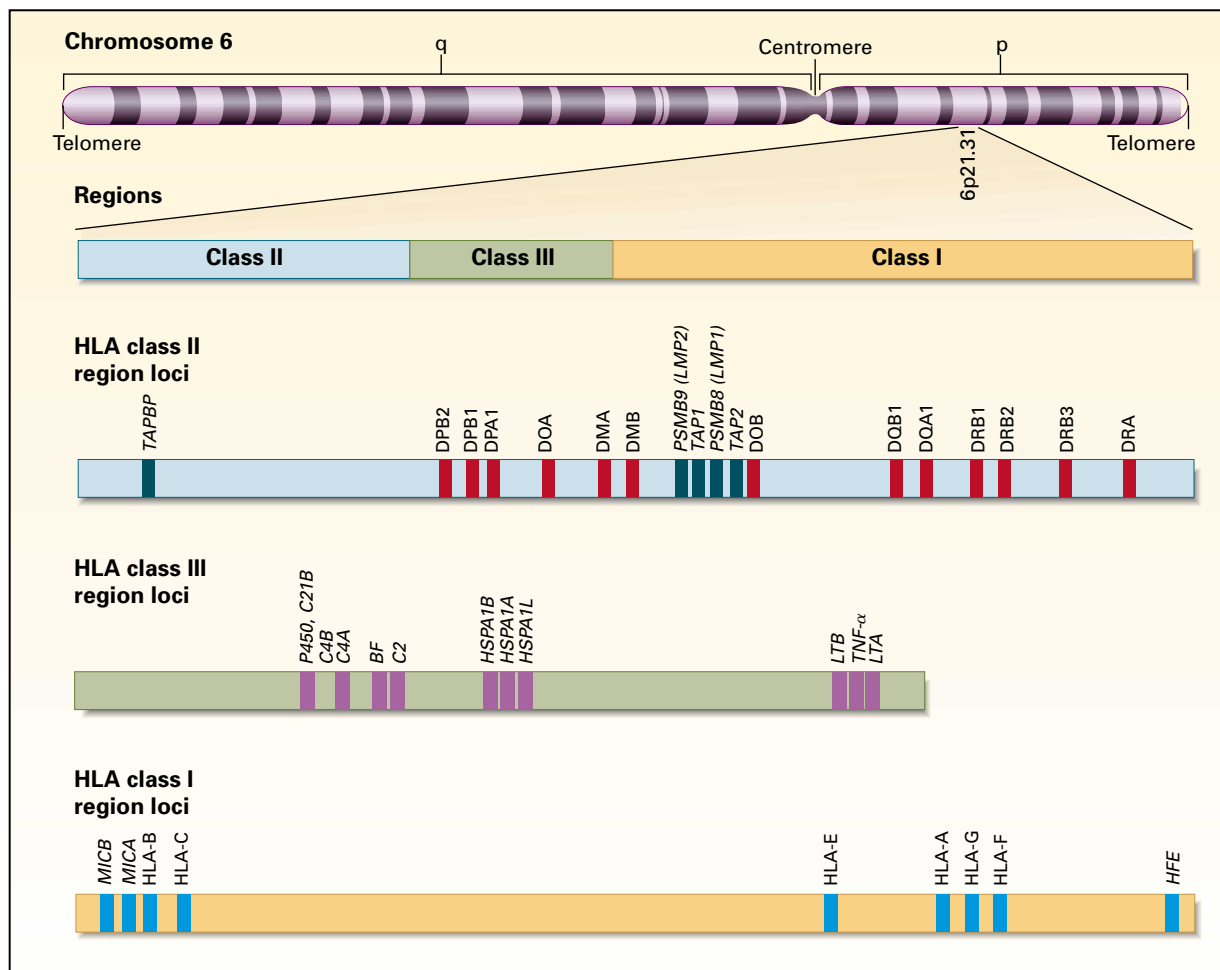
Figure 1. Location and Organization of the HLA Complex on Chromosome 6.

The complex is conventionally divided into three regions: I, II, and III. Each region contains numerous loci (genes), only some of which are shown. Of the class I and II genes, only the expressed genes are depicted. Class III genes are not related to class I and class II genes structurally or functionally. *BF* denotes complement factor B; *C2* complement component 2; *C21B* cytochrome P-450, subfamily XXI; *C4A* and *C4B* complement components 4A and 4B, respectively; *HFE* hemochromatosis; *HSP* heat-shock protein; *LMP* large multifunctional protease; *LTA* and *LTB* lymphotoxins A and B, respectively; *MICA* and *MICB* major-histocompatibility-complex class I chain genes A and B, respectively; *P450* cytochrome P-450; *PSMB8* and *9* proteasome β 8 and 9, respectively; *TAP1* and *TAP2* transporter associated with antigen processing 1 and 2, respectively; *TAPBP* TAP-binding protein (tapasin); TNF-α tumor necrosis factor α; and *HSPA1A, HSPA1B,* and *HSPA1L* heat-shock protein 1A A-type, heat-shock protein 1A B-type, and heat-shock protein 1A–like, respectively.

cytoplasm. The bags are then pinched off as endocytic vesicles, and they fuse with primary lysosomes, which are loaded with an assortment of proteolytic enzymes, to form endosomes.[5] Within the endosomes, the ingested proteins are degraded, first to peptides and then, in some vesicles, into amino acids for reuse.

This mode of protein processing must have evolved at an early stage in the history of living forms. Later, the jawed vertebrates found a new use for it by enlisting it in the defense of the body against pathogens. Normally, the proteins that undergo recycling are the organism's own, but in infected cells, proteins originating from the pathogen are also routed into the processing pathways. With the exception of jawed vertebrates, no organisms appear to make a distinction between peptides derived from their own (self) proteins and those derived from foreign (nonself) proteins. Jawed vertebrates, by contrast, use the peptides derived from foreign (usually microbial) proteins to mark infected cells for destruction.

In an uninfected cell, "housekeeping" proteasomes continuously churn out self peptides, some of which are picked up by molecules called "transporters associated with antigen processing," or TAPs, encoded by the *TAP1* and *TAP2* genes.[5] The TAP1 and TAP2
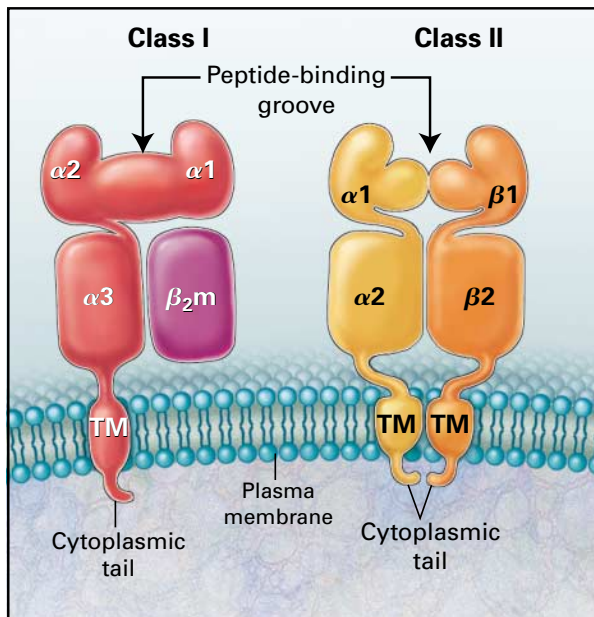
Figure 2. Structure of HLA Class I and Class II Molecules.
Beta$_2$-microglobulin (β_2m) is the light chain of the class I molecule. The α chain of the class I molecule has two peptide-binding domains (α1 and α2), an immunoglobulin-like domain (α3), the transmembrane region (TM), and the cytoplasmic tail. Each of the class II α and β chains has four domains: the peptide-binding domain (α1 or β1), the immunoglobulin-like domain (α2 or β2), the transmembrane region, and the cytoplasmic tail.
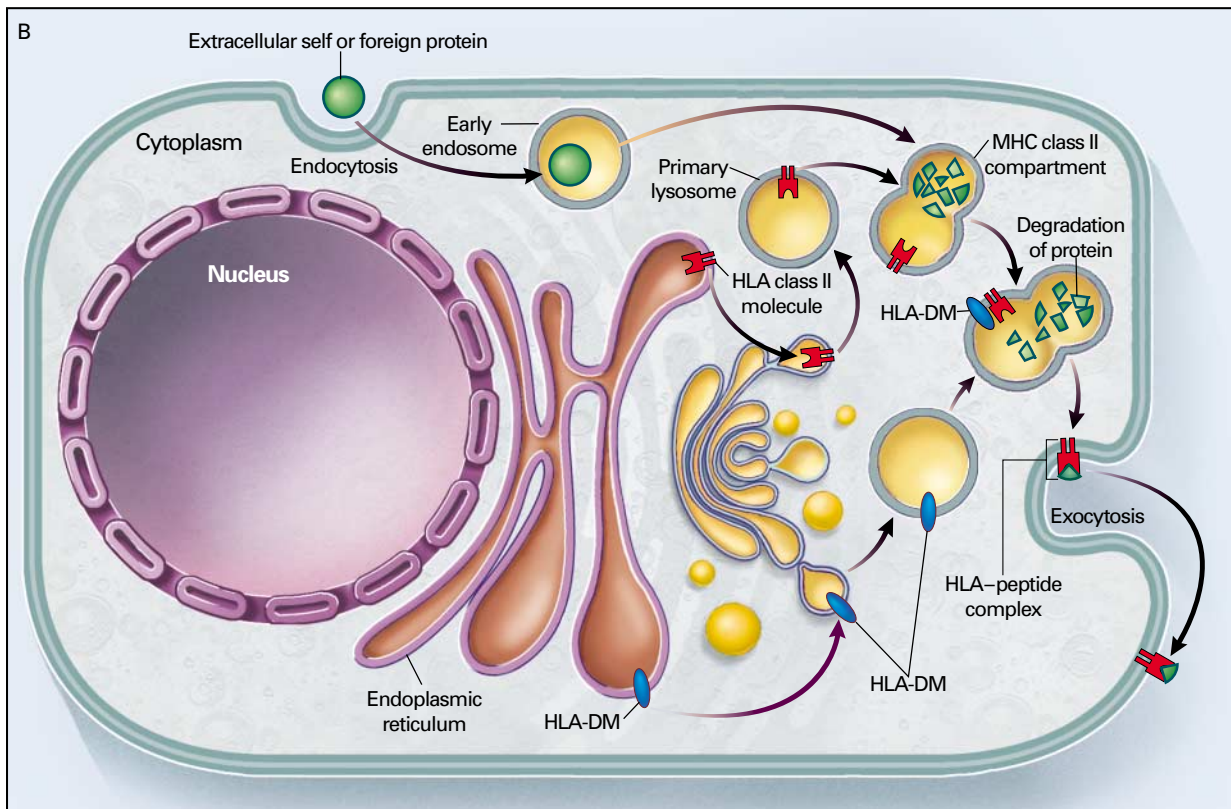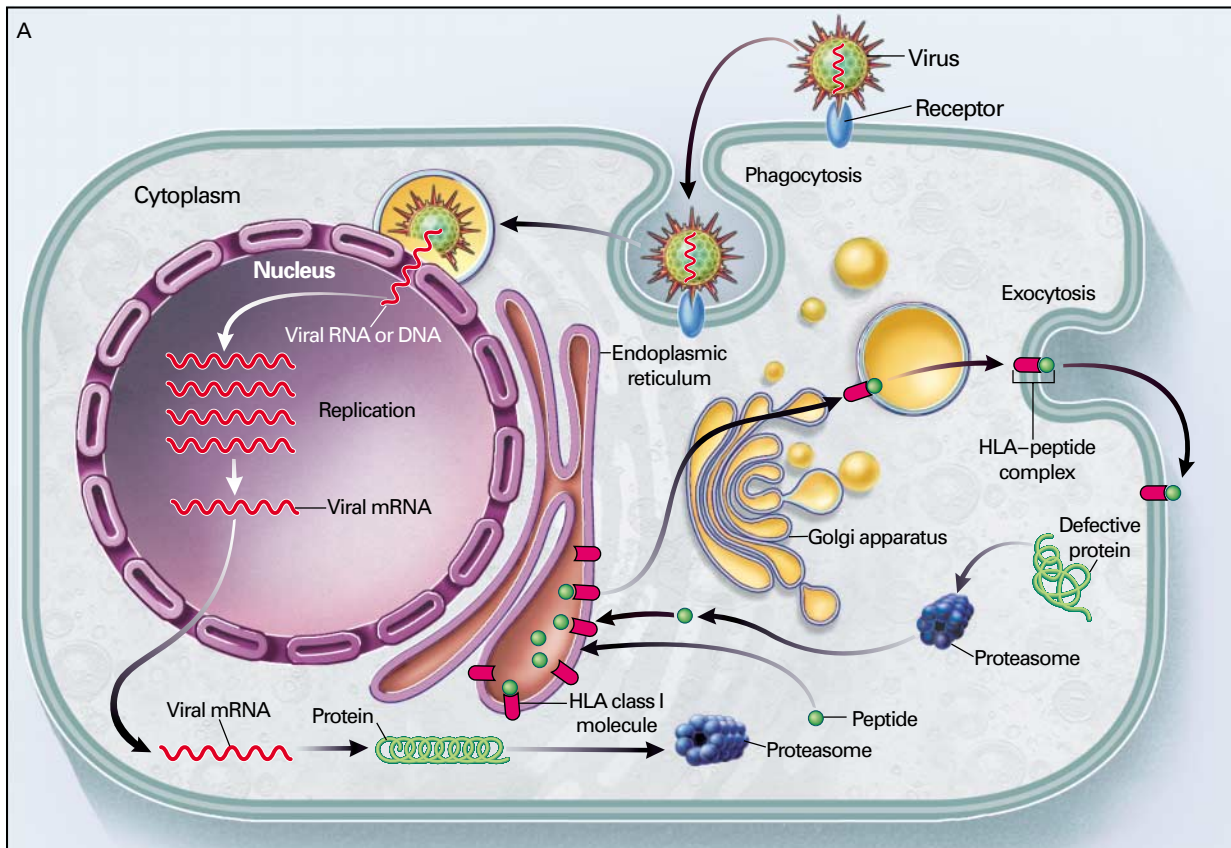
proteins interact to form a channel for transporting peptides across the membrane of the endoplasmic reticulum. Peptides released by proteasomes bind to the cytosolic surface of the TAP molecule and are ferried through this channel. On the luminal surface of the endoplasmic reticulum, queuing up like trucks waiting to be loaded with cargo, are the class I molecules (Fig. 3A). The two polypeptide chains of the class I molecules, the α chain and the beta$_2$-microglobulin, are manufactured separately on ribosomes attached to the cytosolic surface of the endoplasmic reticulum, but as they come off the assembly line, they thread through special channels to make their way to the luminal surface of the endoplasmic reticulum. There, the emerging chains are attended by a suite of molecular chaperones — calnexin, calreticulin, endoplasmic reticulum p57, TAP-binding protein (also referred to as tapasin), and perhaps others — which ensure that the polypeptides do not fold prematurely, that they are properly glycosylated, that the α chain meets beta$_2$-microglobulin at the appropriate time, and that when this moment comes, the union proceeds without a hitch. A class I molecule is then pinioned by the TAP-binding protein to the TAP molecule for loading. When a suitable peptide emerges from the TAP channel, the peptide-binding groove (Fig. 2) of the waiting class I molecule snags it. The loaded molecule then undocks from the complex of TAP-binding protein and TAP and sets off on a journey to the surface of the cell. There, the class I molecule remains anchored in the plasma membrane by the transmembrane region of the α chain. In this position, it displays the bulk of the α chain (the α1, α2, and α3 domains shown in Fig. 2), the peptide, and the associated beta$_2$-microglobulin to other cells.

In the meantime, the class II molecules are also preparing to receive peptides generated by the endocytic protein-processing pathway (Fig. 3B).[5] Like the two chains of class I molecules, those of class II molecules are manufactured separately on the cytosolic surface of the endoplasmic reticulum and then brought together, folded, and assembled on the luminal surface of the structure with the assistance of chaperones. Unlike class I molecules, however, class II molecules are not loaded with peptides in the endoplasmic reticulum. Instead, they associate with a protein produced in the endoplasmic reticulum, the invariant chain, part of which acts as a stopper for the peptide-binding groove and thereby precludes premature loading of peptides. Enclosed in membranous vesicles, the complexes of class II molecules and invariant chains journey to the region of the cytoplasm in which they intersect with endosomes with their cargo of exogenous proteins.[5] The transporting vesicles and the endosomes fuse to form the MHC class II compartment, in which proteases degrade the exog-

Figure 3 (facing page). Antigen Processing.
Panel A shows the principal pathways of generating peptides for loading onto HLA class I molecules. Worn-out or defective proteins in the cytosol are degraded into peptides in proteasomes. Selected peptides are then transported into the endoplasmic reticulum, where they are loaded onto newly synthesized class I molecules. The HLA–peptide complexes are exported by way of the Golgi apparatus to the surface of the cell. In tissues infected with a virus, viral particles are taken up by cells and uncoated. The viral DNA or RNA enters the nucleus and replicates within it. The viral messenger RNA (mRNA) then enters the cytosol and is transcribed into proteins. Some of the proteins are subsequently degraded in proteasomes, and the peptides are delivered into the endoplasmic reticulum, where they are loaded onto class I molecules for export to the surface of the cell. Panel B shows the processing of extracellular proteins. Self or foreign proteins are taken up by endocytosis (or phagocytosis) and sequestered into endosomes. Class II molecules synthesized in the endoplasmic reticulum are delivered by way of the Golgi apparatus into primary lysosomes, which fuse with the early endosomes to form the major-histocompatibility-complex (MHC) class II compartment. Enzymes brought into this compartment by the lysosomes degrade the engulfed proteins into peptides. HLA-DM molecules synthesized in the endoplasmic reticulum and delivered into the MHC class II compartment by transport vesicles help load the peptides onto the class II molecules. The HLA–peptide complexes are then exported to the surface of the cell.

A

Virus

Receptor

Phagocytosis

Exocytosis

Cytoplasm

Nucleus

Viral RNA or DNA

Endoplasmic
reticulum

Replication

HLA–peptide
complex

Viral mRNA

Golgi apparatus

Defective
protein

Proteasome

Viral mRNA   Protein   HLA class I
molecule

Peptide

Proteasome

B

Extracellular self or foreign protein

Cytoplasm

Early
endosome

MHC class II
compartment

Primary
lysosome

Endocytosis

Nucleus

Degradation
of protein

HLA class II
molecule

HLA-DM

HLA-DM

Exocytosis

HLA–peptide
complex

Endoplasmic
reticulum

HLA-DM

HLA-DM

enous proteins and the bulk of the invariant chain (the class II molecules being remarkably resistant to the action of these enzymes). This process leaves behind the piece of the invariant chain that functions as a stopper in the peptide-binding groove. Ultimately, however, the stopper is also dislodged by class II molecules specialized in this task (HLA-DM), and a peptide derived from an exogenous protein slips into the groove. The peptide-laden class II molecules are then exported to the surface of the cell.

Protein processing and loading of peptides onto class I molecules are taking place all the time in most cells. There is always plenty of material to feed the processing machinery, because worn-out, damaged, and misfolded proteins are continuously being degraded and replaced by new ones. In addition to processing by proteasomes, some proteins are also degraded into peptides by soluble enzymes in the cytosol.[6]

By contrast, the processing of exogenous proteins and the loading of peptides onto class II molecules are normally restricted to B cells, macrophages, and dendritic cells, which are very efficient in taking up material by endocytosis or phagocytosis. Although most class I and class II molecules form complexes with peptides derived from endogenous and exogenous proteins, respectively, this demarcation is by no means absolute. Class I molecules containing peptides derived from exogenous (e.g., bacterial) proteins and class II molecules laden with peptides generated from endogenously synthesized (e.g., viral) proteins exist, but how these complexes arise is not entirely clear.[5]

The consequence of protein processing is that the surfaces of cells become adorned with peptide-laden HLA molecules, amounting on a per cell basis to roughly 100,000 to 300,000 class I or class II products of each of the highly expressed HLA loci.[7] Since each HLA molecule has one peptide bound to it, each uninfected cell displays hundreds of thousands of self peptides on its surface. Some of these peptides are present in the thousands, whereas others are represented by a few copies; most peptide species have 100 or so copies on the surface of each cell. Each cell thus displays a heterogeneous collection of peptides, and the surface of a cell resembles rows of well-stocked stalls at a bazaar, with bargain hunters scrutinizing the wares. But if, in this metaphor, the vendors are the HLA molecules and the peptides the goods, who are the potential buyers? They are a group of lymphocytes reared in the thymus and then turned loose to roam the body — the T cells.

HLA AND SELECTION IN THE THYMUS

The lymphocyte progenitors entering the thymus are programmed to die unless they receive signals instructing them to differentiate further.[8] These signals emanate from an interaction that involves the epithelial component of the thymus and several species of molecules, two of which are critical: the T-cell receptor[9] and the CD4–CD8 coreceptors.[10] The ligands for both are the HLA–peptide complexes, but the T-cell receptor engages the peptide and the peptide-binding part of the HLA molecule, whereas the CD4–CD8 coreceptors interact with parts outside the peptide-binding groove.

Maturing thymocytes express both CD4 and CD8 molecules (i.e., they are CD4+CD8+), but the engagement of these cells with HLA molecules causes the down-regulation of one and the up-regulation of the other, resulting in mature T cells of either the CD4+CD8− type or the CD4−CD8+ type.[11] Which of the two CD molecules the cell ultimately expresses is determined by the T-cell receptor. Some T-cell receptors interact preferentially with class I and others with class II molecules, depending on the specificity of their variable (V) domains, in particular the germ-line–encoded complementarity-determining regions 1 and 2 (CDR1 and CDR2, respectively) borne by the α chain.

The T-cell–receptor molecule consists of two polypeptide chains, α and β, each of which has a variable and a constant domain. In the V domain, the highest degree of amino acid variability is concentrated in three segments: CDR1, CDR2, and CDR3. The names of these regions refer to the fact that in the three-dimensional depiction of the molecule, they form loops that project like fingers from a grasping hand to grip the HLA–peptide complex according to the principle of spatial complementarity. The variability of CDR1 and CDR2 is inherited through the germ line, whereas that of CDR3 is largely generated somatically during the maturation of each T cell.

The ability of the T-cell receptor to discriminate between class I and II molecules is so refined that the replacement of a single amino acid at a critical position in the receptor's Vα region can change the specificity of the T-cell receptor from one HLA class to the other.[12] A thymocyte whose T-cell receptor engages a complex of an HLA class I and a peptide generally also engages its CD8 coreceptors and down-regulates the expression of the unengaged CD4 molecules. The reverse happens to a thymocyte whose T-cell receptor has engaged a complex of an HLA class II molecule and a peptide: it becomes a CD4+ cell. Restriction of the maturing T cells to the expression of either CD4 or CD8 molecules is accompanied by the specification of a developmental program and thus, ultimately, determination of the function of the cell. Generally, CD4+ T lymphocytes become helper T cells that elicit responses from B cells and macrophages, whereas CD8+ T lymphocytes become cytotoxic T cells capable of eliminating target cells identified by the interaction of the T-cell receptor and the HLA–peptide complex.[2]

As progenitor cells enter the thymus and proceed toward the center, dividing and differentiating along the way,[11] they express their T-cell receptor genes in

such a way that each clone produces a receptor specific for a different ligand. As they enter the thymic cortex, thymocytes are given the opportunity to match their newly formed receptors with the abundant HLA–peptide complexes on cortical epithelial cells. Most of these thymocytes do not find ligands that fit the combining sites of their receptors, and since this means that they receive no signal to justify their further existence, they die "by neglect." Only a minority of thymocytes capable of weakly (i.e., with a low affinity) engaging their receptors with HLA–peptide complexes receive a signal that blocks the pathway to apoptosis (i.e., they undergo positive selection).[11] The interaction is not strong enough to hold the thymocyte to a cortical epithelial cell, and after they have disengaged, the thymocyte moves deeper into the thymus.

At the corticomedullary junction and then in the medulla, thymocytes run into hordes of macrophages and dendritic cells (which together are the antigen-presenting cells) that display large quantities of HLA–peptide ligands. The thymocytes are given a second chance to find a match for their receptors, but the setting in which this new trial takes place has changed. These medullary antigen-presenting cells are not just passive displayers of HLA–peptide complexes; they also express molecules that provide costimulatory signals to the maturing thymocytes.

Medullary antigen-presenting cells not only express costimulatory molecules that differ from those of the cortical epithelial cells but also express different proteases (cathepsins) in their lysosomes by which they process the invariant chain and other proteins.[13] As a consequence of these and other differences, a stronger interaction (i.e., one with a higher affinity) between T-cell receptors and HLA–peptide ligands becomes possible, and when it takes place, it generates a signal instructing the thymocytes to undergo apoptosis. In this manner, the population of medullary thymocytes is purged of most self-reactive cells that might otherwise initiate an autoimmune response (i.e., it undergoes negative selection).[11]

Cells that survive both positive and negative selection leave the thymus and enter the periphery as naive T cells. Of all the progenitor cells that enter the thymus and proliferate in it, less than 1 percent mature into T cells. In the periphery, naive T cells are probably kept alive by low-affinity interactions with complexes of HLA molecules and self peptides. During an infection, T cells that bind to complexes of HLA molecules and foreign peptides with high affinity are stimulated to initiate an immune response. Thus, high-affinity interactions between T-cell receptors of immature cells in the thymus lead to apoptosis, whereas in the periphery they result in cellular proliferation. The mechanisms responsible for this difference in behavior remain unidentified.

Once a few hundred of the more than 10,000 re-

ceptors displayed by a single T cell become engaged by a ligand, the T cell is activated to differentiate either into a CD8+ cytotoxic killer T cell (if the engaging HLA molecule is of the class I type) or into a CD4+ helper T cell (if the engagement involves a class II molecule).[14] The activities of the stimulated helper T cell include the production of interferon-γ, along with other cytokines.

Interferon-γ binds to the regulatory regions of selected genes, including the class II genes and loci that control specialized subunits of proteasomes. The binding enhances the expression of these genes, increasing the number of class II molecules on antigen-presenting cells and altering the composition of the subunits of proteasomes.[5,15] These modified "immunoproteasomes" are more effective than housekeeping proteasomes at generating peptides for loading onto the class I molecules. Both processes enhance the ongoing immune response.

INTERACTIONS BETWEEN T-CELL RECEPTORS AND COMPLEXES OF HLA MOLECULES AND PEPTIDES

The peptide-binding groove of an HLA molecule consists of two parts, a floor and two walls (Fig. 4). In the floor, the α chain of the class I molecule or the α and β chains of the class II molecule meander to form a rather flat structure, the β-pleated sheet. In each of the two walls, the chain is coiled into an α helix. In the class I peptide-binding groove, the ends of the α helices of the α1 and α2 domains converge to close the groove,[16] whereas in the class II molecules, the groove is open-ended.[17] Consequently, the closed class I groove accommodates shorter
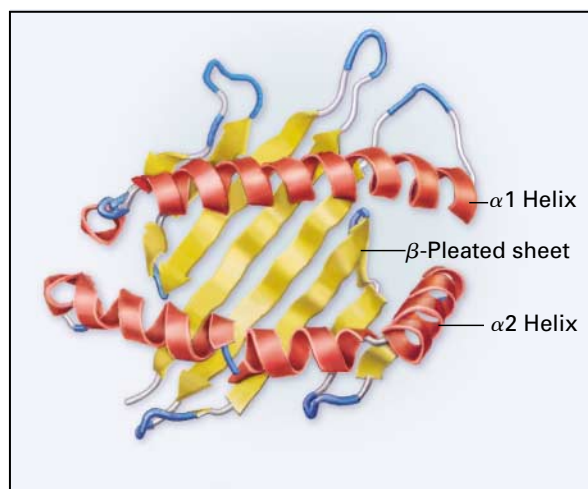

Figure 4. Ribbon Model of the Tertiary Structure of an HLA Class I Peptide-Binding Module.

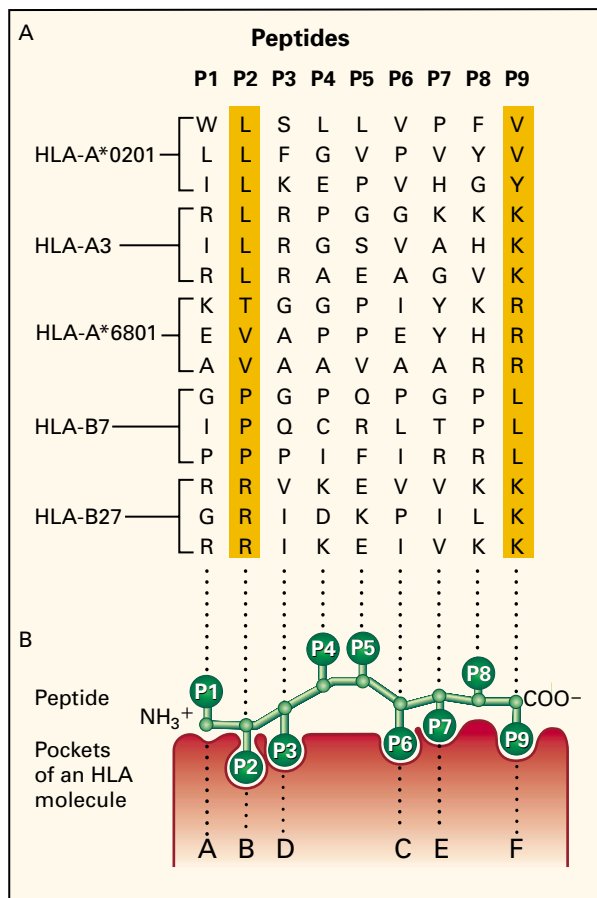The model is shown from the top. The β-pleated sheets are composed of the α chain.

Figure 5. Interactions between HLA Molecules and Peptides.

Panel A shows examples of peptide motifs. The listed nonamers, as well as many others,[7] have been found in complexes with the indicated HLA class I molecules. The anchor residues are highlighted in yellow. In Panel B, a longitudinal section through the peptide-binding groove of an HLA class I molecule, the side chains of amino acid residues composing the bound peptide (P1 through P9) are oriented either down into the pockets of the HLA molecule or up. The following amino acids are shown: alanine (A), cysteine (C), aspartic acid (D), glutamic acid (E), phenylalanine (F), glycine (G), histidine (H), isoleucine (I), lysine (K), leucine (L), proline (P), glutamine (Q), arginine (R), serine (S), threonine (T), valine (V), tryptophan (W), and tyrosine (Y).

Figure 6. Interactions between a T-Cell Receptor and the HLA–Peptide Complex.

Panel A shows the diagonal orientation of the T-cell receptor on the surface of the HLA–peptide complex. Panel B shows the bridge between a T cell and the antigen-presenting cell created by the interaction between the T-cell receptor and the HLA–peptide complex. Complementarity-determining region 1 of the α and β chains of the T-cell receptor is not visible in this depiction because one is positioned behind and the other in front of the part shown. Beta$_2$-microglobulin (β_2m) is the light chain of the class I molecule. The three complementarity-determining regions (CDR1, CDR2, and CDR3) are shown.

peptides (7 to 15 residues long) than the open class II groove; the longer ones either buckle up in the middle or, much less frequently, hang over the wall at one end. The orientation of the bound, stretched-out peptides is fixed: their N terminals are always positioned at the same end of the groove as defined by the orientation of the HLA polypeptide chains, with the C terminals at the opposite end.

The side chains of the amino acid residues in the middle of the peptide protrude out of the groove, whereas those of most of the remaining residues point into the groove and are housed in specialized small
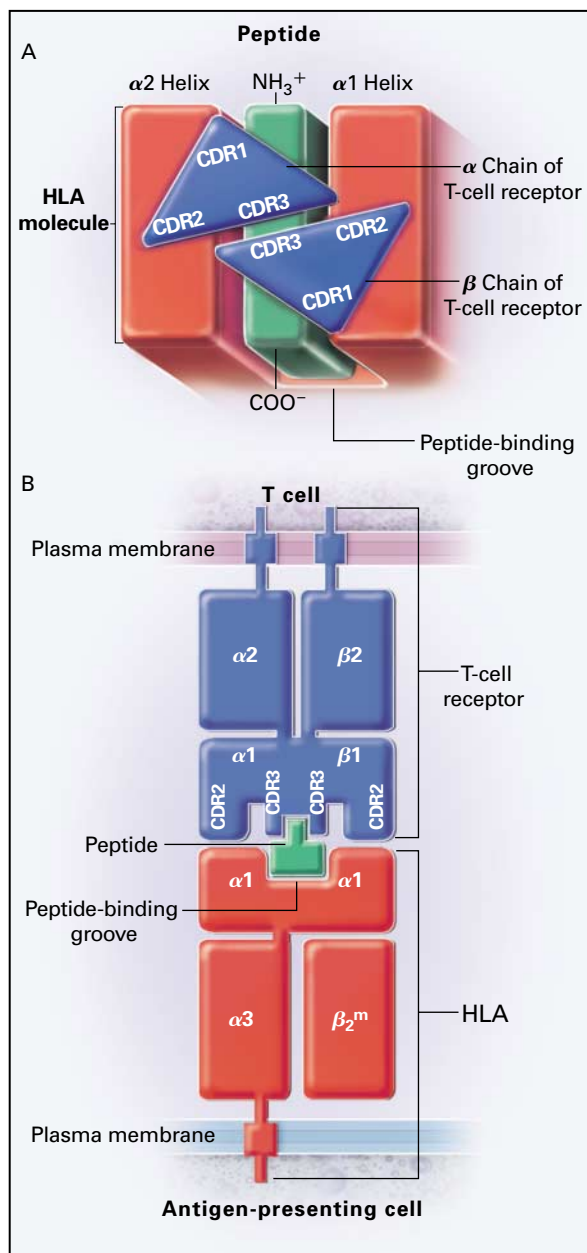
cavities, or pockets, in the groove's floor.[16,18] Typically, an HLA class I molecule has six pockets (A through F) distributed along the length of the groove (Fig. 5). Two or three of the pockets (in HLA-A, B, or C molecules, usually pockets B and F) are particularly influential in determining which peptide a molecule binds, because the side chains that fit into them serve as the peptide's anchors.[7] The remaining pockets are less important in determining the binding specificity. The residues lining the pockets are encoded in genetic segments defined by the individual alleles of the HLA genes.

The product of a particular allele is capable of binding any one of a large number of peptides, generally thousands of ligands.[19] The peptides differ in their sequences but share two or three amino acid residues (a motif) that fit into the anchoring pockets (referred to as anchor residues).[7,20] The demands with regard to the sharing of residues by the remaining pockets are generally less stringent. Peptides that bind to different allelic products are distinguished by their motifs (Fig. 5). The interaction of peptides with class II molecules is governed by similar principles.[7,20]

Viewed from the top (Fig. 6A), the peptide-binding groove presents a rather flat surface bordered by the α helixes of the HLA molecule, with the peptide in the middle. This is the surface with which the T-cell receptor interacts. The receptor positions itself diagonally over the surface, with the CDR1 and CDR2 loops of the T-cell receptor α chain hovering over the N-terminal half of the peptide and the CDR1 and CDR2 loops of the T-cell receptor β chain looming over the peptide's C-terminal part.[21-24] The centrally located CDR3 loops of the α and β chains of the T-cell receptor touch most of the protruding side chains of the peptide (Fig. 6B). The less variable CDR1 and CDR2 loops interact primarily with the relatively conserved amino acid residues of the HLA α helixes, whereas the more variable CDR3 loops touch the most variable part of the peptide. Thus, the relatively conserved contacts of the CDR1 and CDR2 loops with the HLA molecule establish the overall orientation and configuration of the interaction, whereas the highly variable contacts of the CDR3 loops with the peptide determine the specificity of the interaction.

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