CHAPTER 19

MHC and MHC-Like Molecules: Structural Perspectives on the Design of Molecular Vaccines

Vasso Apostolopoulos,* Eliada Lazoura and Minmin Yu

Abstract

Major histocompatibility complex (MHC) molecules bind and present short antigenic peptide fragments on the surface of antigen presenting cells (APCs) to T-cell receptors. Recognition of peptide-MHC complexes by T-cells initiates a cascade of signals in T-cells and activated cells either destroy or help to destroy the APC. The MHCs are divided into three subgroups: MHC class I, MHC class II and MHC class III. In addition, nonclassical MHC molecules and MHC-like molecules play a pivotal role in shaping our understanding of the immune response. In the design of molecular vaccines for the treatment of diseases, an understanding of the three-dimensional structure of MHC, its interaction with peptide ligands and its interaction with the T-cell receptor are important prerequisites, all of which are discussed herein.

Introduction

The Major Histocompatibility Complex (MHC) is a set of molecules displayed on cell surfaces that is responsible for antigen presentation to lymphocytes. The MHC molecules control the immune response through "self" and "non self" recognition and consequently serve as targets in transplantation rejection. More than two decades of intense research were required to determine the function of MHC molecules in antigen presentation. In the early 1970s, neither the function of the T-cell receptor (TCR) nor its ligand were known. The interaction between the MHC and antigen was also unclear. MHC restriction was only established in the early 1970s with the discovery that MHC molecules control T helper cells and B-cells,1 T helper cells and macrophages,2 as well as CD8 T-cell recognition of target cells.3 It was demonstrated that T-cells recognize antigenic peptides in the context of MHC; and consequently, T-cells were said to be MHC restricted.

The MHC multigene clusters are located on chromosome 17 in mice and chromosome 6 in humans. The MHC molecules are divided into three subgroups: MHC class I, MHC class II and MHC class III. The MHC class I locus encodes heterodimeric peptide-binding proteins as well as antigen processing molecules, such as TAP and tapasin. The MHC class II locus encodes heterodimeric peptide-binding proteins and proteins that modulate peptide loading onto MHC class II proteins in the lysosomal compartment, such as MHC class II DM, -DQ and -DP. MHC class I proteins are expressed on all nucleated cells and MHC class II are found on only a few specialized cell types; B-cells, neutrophils, dendritic cells and thymic epithelial cells and can be induced on macrophages and human T-cells. The MHC class III locus encodes for other immune

*Corresponding Author: Vasso Apostolopoulos—Burnet Institute at Austin, Kronheimer Building, Studley Road, Heidelberg, VIC 3084, Australia. Email: vasso@burnet.edu.au

components, i.e., complement components (C2, C4, factor B), cytokines (TNF-α and TNF-β) and HSP70.

**Stimulation of CD8 T Cells**

MHC, first described more than 70 years ago to control transplant rejection in mice, was initially termed H-2. There are three gene families for murine MHC class I: H-2K, H-2D and H-2L and for human MHC: HLA-A, HLA-B and HLA-C. The first step in CD8+ T-cell generation is the uptake and presentation of peptides by antigen presenting cells through their MHC molecules. Peptides bound to MHC class I are usually endogenous and cytosolic although exogenous peptides may also be presented by MHC class I molecules.5 Exogenous antigens are taken up by antigen presenting cells (APCs), primarily dendritic cells, into phagosomes and early and late endosomes and presented to MHC class II molecules. Numerous reports have demonstrated that in early endosomes some antigens can either degrade or escape out of the endosome into the cytosol and enter the proteasome. From this point, exogenous- and endogenous-derived peptides follow the same pathway. The proteasome consists of 24 subunits, half of which contain proteolytic activity. The proteasome degrades antigens (proteins) into small peptides which are released into the cytosol. The peptides are transported from the cytosol into the endoplasmic reticulum (ER) via the transporter associated with antigen processing (TAP1 and TAP2) by ATP. In the ER, peptides bind to the newly synthesized MHC class I molecules following the formation of a large multimeric complex which involves TAP, tapasin, calreticulin, calnexin and ER60. From the ER, the peptide-MHC class I complex is transported to the surface of APCs through the secretory pathway (Golgi) where the complex undergoes several posttranslational modifications. Then the peptide-MHC class I complexes expressed at the APC surface interact with the T-cell antigen receptors (TCRs) of CD8 T-cells. In the late 1980s and early 1990s, the first reported crystal structures of human and murine MHC class I molecules with bound peptides provided structural insights on how the MHC specifically binds and presents antigenic peptides to T-cells.

**MHC Class I Molecules**

The first X-ray structure of an MHC class I molecule, the human HLA-A2, was determined in 1987. To date more than 150 peptide-bound MHC structures are available, including human HLA-A1, HLA-A2, HLA-A3, HLA-A11, HLA-B27, HLA-A31, HLA-Aw68, HLA-B35, HLA-B53, HLA-B44 and HLA-57, as well as murine H-2Kb, H-2Dd, H-2Ld and H-2Kb. The H-2 and HLA molecules consist of a glycosylated 45 kDa (340 amino acids) heavy α chain which is noncovalently associated with the nonglycosylated 11.6 kDa (96 amino acids) β2-microglobulin (Fig. 1). The heavy and light chains exist in the MHC in a 1:1 ratio. The heavy chain anchors the MHC complex into the cell membrane and is divided into three extracellular domains (α1, α2, α3; 90 amino acids each), a hydrophobic transmembrane region (30 amino acids) and a short cytoplasmic tail (30 amino acids). The α1 domain is membrane bound and interacts with CD8. Both the α chain and the β2-microglobulin are members of the Ig superfamily and share a disulfide-bonded domain structure with antibody. Peptides are closely associated with the MHC by specific interactions in the peptide binding groove (eight-stranded β-pleated sheet floor) which is located between the α1 and α2 helices, forming a cleft (Fig. 1). A long groove between the helices constitutes the binding site for processed peptides. The side chains of peptides, i.e., anchor residues, fit into specificity pockets that extend along the floor of the groove. The peptide-binding groove is subdivided into various pockets (A-F). The amino acid sequence between the α1 and α2 helices varies from allele to allele, thus, changing the specificity of the peptide binding groove. The cleft is closed at the ends, limiting the size of suitable peptides to 8-10 amino acids. Peptides are held by hydrogen bonds at the N- and C-termini and by binding to the specificity pockets which anchor the peptide in the groove (Fig. 1). The anchor residues slightly vary between MHC alleles, whereas non-anchor amino acids vary considerably, thus allowing numerous peptides to be presented by a few MHC class I alleles. The non-anchor amino acids are known to interact with the