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HLA-B polymorphisms and intracellular assembly modes

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ABSTRACT

Human leukocyte antigen (HLA) class I molecules are ligands for antigen receptors of cytotoxic T cells (CTL) and inhibitory receptors of natural killer (NK) cells. The high degree of HLA class I polymorphism allows for the selection of distinct and diverse sets of antigenic peptide ligands for presentation to CTL. The extensive polymorphisms of the HLA class I genes also result in large variations in their intracellular folding and assembly characteristics. Recent findings indicate that North American HLA-B variants differ significantly in the stabilities of their peptide-deficient forms and in the requirements for the endoplasmic reticulum (ER)-resident factor tapasin for proper assembly. In HIV-infected individuals, the presence of tapasin-independent HLA-B allotypes links to more rapid progression to death. Further studies are important to better understand how the intrinsic structural characteristics of HLA class I folding intermediates affect immune responses mediated by CTL and NK cells.

1. MHC class I molecules as ligands for cytotoxic T cell (CTL) and natural killer (NK) cell receptors

Major histocompatibility complex (MHC) class I molecules are ligands for antigen receptors of $CD8^+$ CTL (Bjorkman, 1997; Rossjohn et al., 2014) and for inhibitory receptors of natural killer (NK) cells (Parham and Moffett, 2013). In a normal healthy cell, MHC class I heavy chains and light chains (β2-microglobulin; β2m) form heterodimers that bind short peptides derived from self-proteins. In cells infected with an intracellular pathogen or in cancer cells, a subset of the cellular peptides bound to MHC class I molecules are replaced by pathogen-derived or tumor-specific peptide sequences, which can trigger the activation of T cell receptors (TCR) of specific CTL. Cell surface MHC class I molecules also engage selected inhibitory receptors of NK cells, thereby maintaining NK cells in a quiescent state (Li and Mariuzza, 2014). Viruses and cancers that interfere with the assembly and cell surface expression of MHC class I molecules reduce the engagement of inhibitory receptors, thereby driving NK cells towards activation. Thus, MHC class I molecules are key regulators of the activation of two major subsets of immune cells.

Three sets of genes encode human and mouse MHC class I heavy chains; these are respectively human HLA-A, HLA-B and HLA-C and murine H2-K, H2-L and H2-D. Human MHC class I genes, encoded on chromosome 6, are highly polymorphic. The HLA-B locus is the most polymorphic. Based on current estimates, there are over 3000 allelic variants of HLA-B (Robinson et al., 2015). The heavy chains of MHC class I molecules comprise three domains; α1 and α2, which contain a peptide-binding groove formed by anti-parallel β−strands that are topped with two helices, and α3, an immunoglobulin(Ig)-like membrane proximal domain (Fig. 1A). β2m also forms an Ig-like domain (Bjorkman, 1997). The majority of polymorphic residues are located within the peptide binding grooves of MHC class I molecules (for example, those depicted in Fig. 1B) and determine the specificities for peptide binding. Each MHC class I variant binds to a large number of peptides with common sequence motifs (Rammensee et al., 1999), called anchor residues, that form specific interactions with MHC class I residues contained within the peptide binding grooves. The peptide binding groove compositions of individual MHC class I allotypes allow for the selection of peptides with distinct sequence motifs. Expression of MHC class I alleles is co-dominant, and because of the high degree of polymorphism of the HLA-A, HLA-B and HLA-C genes, most humans are heterozygous at each locus. Thus, human cells typically express six different MHC

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class I variants to enable presentation of a diverse set of peptide antigens to CTL. Antigen receptors of CTL, TCRs, have extracellular domains that resemble antibody Fab regions in their overall structure (Bjorkman, 1997; Rossjohn et al., 2014). Like antibodies, TCRs contain variable domains that are generated during T cell development by the recombination of multiple gene segments. Hypervariable loops of the TCR variable domains interact with the α1 and α2 domains of the MHC class I heavy chain as well as with bound peptide (Fig. 1A). TCRs are exquisitely specific for particular MHC class I-peptide combinations (Bjorkman, 1997; Rossjohn et al., 2014).

Antigen recognition by NK cells is driven by the net balance of signals emanating from the engagement of activating and inhibitory NK cell receptors. The inhibitory NK receptors that engage MHC class I molecules are structurally distinct in mice and humans. Murine Ly49 receptors belong to the lectin superfamily, whereas human killer-cell immunoglobulin-like receptors (KIR) are members of the immunoglobulin superfamily (Li and Mariuzza, 2014). The human KIR gene family is encoded on chromosome 19 within the leukocyte receptor complex (LRC). There are four phylogenetically distinct lineages of KIR, with lineage II and III KIRs bearing specificity for polymorphic MHC class I molecules (Parham and Moffett, 2013). Among lineage II KIRs, KIR3DL1 recognizes HLA-B molecules and a few HLA-A molecules containing a "Bw4" epitope, which is a specific sequence motif contained within residues 77–83 of the heavy chain (Fig. 1A). KIR3DL2 recognizes HLA-A11 and HLA-A3. Lineage III KIRs, KIR2DL1 and KIR2DL2/3, are largely specific for HLA-C variants (Parham and Moffett, 2013). KIR2DL1 recognizes HLA-C molecules with lysine at position 80 (the C2 epitope), whereas KIR2DL2/L3 recognize HLA-C variants with

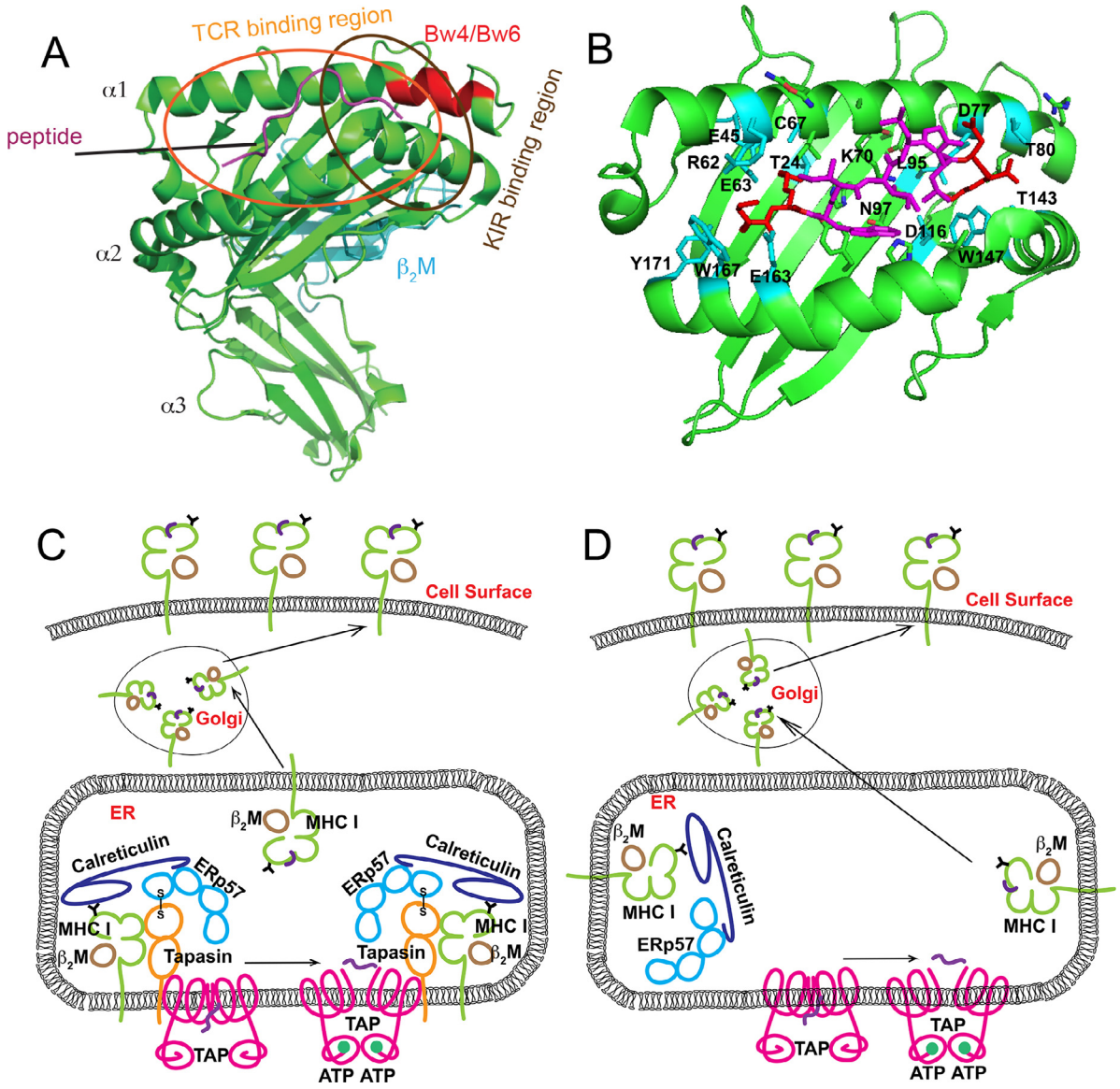

Fig. 1. Structures of MHC class I molecules and their distinct intracellular assembly modes. (A) Structure of HLA-B*2705 (PDB 4G9D), with heavy chains indicated in green and β2m in cyan. The Bw4/Bw6 epitope region is shown in red. Bound peptide (KRWIILGLNK) is indicated in magenta. Approximate TCR and KIR footprints are specified by ovals. (B) Peptide binding groove (α1 and α2 domains) of HLA-B*2705 with bound KRWIILGLNK. Several polymorphic HLA-B*2705 residues important for peptide binding specificity are indicated as sticks. Polymorphic residues interacting with peptide N- and C-termini are shown in cyan. HLA-B*2705 has cysteine, lysine and asparagine respectively at positions 67, 70 and 97. These residues are shown to be important in control of AIDS progression. Bound peptide is shown in magenta and red, with terminal residues colored red and the central residues colored magenta. (C) Conventional tapasin-dependent assembly of HLA-B molecules such as HLA-B*4402 and HLA-B*5701. (D) Tapasin-independent assembly of HLA-B molecules such as HLA-B*3501 and HLA-B*4405. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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