Immunodominance

The Choice of the Immune System

Edited by Jeffrey A. Frelinger

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Cover
Shifts in repertoire and immunodominance following primary and secondary exposures to antigen. For further details see Figure 6.6 on page XXII.

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Contents

Preface

The normal, intact immune system does not have equal probability of responding to every potential part of a protein. It has been known for more than 50 years that only parts of the protein that are "outside" are available for antibody binding. Yet, with the advent of Western blotting techniques, antibodies that react with the interior of the protein have been routinely produced. Although not all epitopes are equally easy to produce, or are equally protective in infection, nearly any structure can be an antibody epitope.

In contrast to antibodies, T cells must recognize fragments of proteins bound to MHC molecules. In T-cell responses against viruses, very few epitopes are easily identified. In the case of LCMV, the immune response in BALB/c mice uses only a single MHC class I protein: L. K and D are not used at all. This is not because there are no suitable peptides that can bind K and D proteins, as BALB/c mice that lack L make an excellent response to LCMV. Furthermore, only a single peptide from the LCMV genome accounts for more than 90% of the CD8 T cells responding to infection. Because LCMV has a coding size of approximately 3500 amino acids, the immune system fixates 9 of 3500 amino acids, or about 0.2% of the coding capacity.

This fixation on a small part of the potential antigenic space is not unique to LCMV in BALB/c mice. Most pathogens in inbred mice show similar immunodominance. Even in response to bacteria, where the pathogen genome size is much larger, dominance is observed. The CD8 T-cell response to Listeria monocytogenes infection is dominated by very few epitopes in both C57Bl/6 and BALB/c mice. With a genome size of almost three million base pairs, the majority of the response is restricted to two or three epitopes. The immune system is choosing only about 0.002% of the coding sequence to recognize.

Why is this so? Clearly, there are many mechanisms at work. In this volume we cover topics including (1) the mechanisms of antigen processing, i.e., how pathogen molecules are converted to molecules that are targets for cell-mediated immunity; (2) binding of processed peptides to MHC molecules, a critical step in their expression on the cell surface; and (3) the role of the pathogen itself in modifying the immune response by interfering with antigen processing and the downstream immune responses.

We have not yet completed the puzzle of immunodominance, but the chapters here represent our current understanding of its pieces.

I thank Andreas Sendtko for encouragement and enthusiasm for this book.

Jeffrey A. Frelinger Chapel Hill, October 2005

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Color Plates

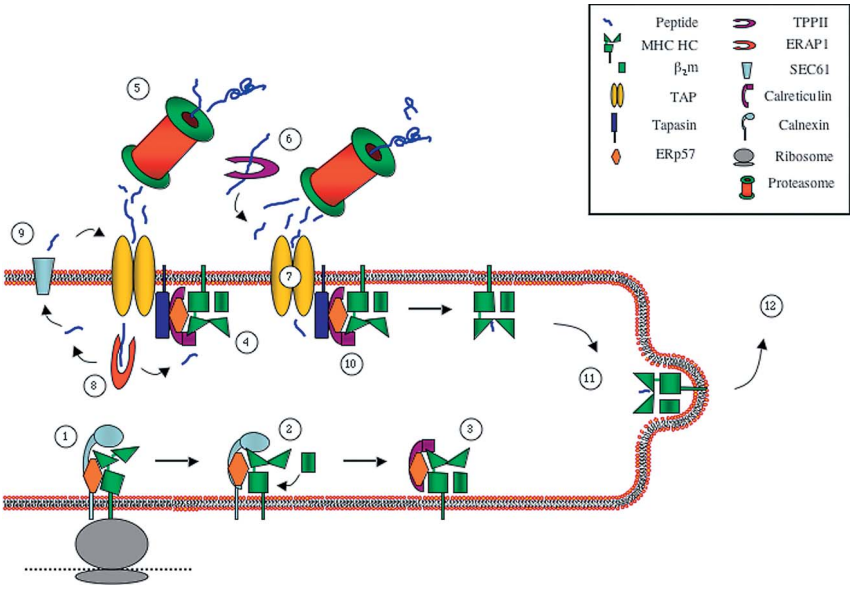


Figure 1.3 Production of peptide-loaded class I MHC. Class I MHC heavy chain and β_2m are translocated separately into the ER. Immediately when accessible, Asn86 of the heavy chain is glycosylated, allowing for recognition by the chaperone calnexin. (1) Calnexin also recruits Erp57, which mediates disulfide bond formation in α3 and α2 of class I heavy chain. (2) Once the heavy chain is folded and the disulfide bond in α3 is formed, soluble β_2m binds to class I heavy chain. While the MHC class I molecule is being formed (cycling on and off calnexin), newly translated tapasin associates with calnexin and ERp57, both of which facilitate its folding and disulfide bond formation. Tapasin with calnexin–ERp57 then binds and stabilizes the TAP1/2 dimer. (3) Upon binding of β_2m, calnexin dissociates and is replaced by calreticulin. The class I heavy chain–β_2m–calreticulin–ERp57 heterocomplex then associates with the tapasin–TAP–calnexin–ERp57 heterocomplex. ERp57 remains part of the peptide-loading complex (PLC) until peptide has been loaded, but it is not known whether ERp57 comes with tapasin or the class I molecule. (4) The PLC now consists of TAP, tapasin, heavy chain, β_2m,

Figure 1.3 (continued)

calreticulin, and ERp57. (5) Proteasomes in the cytosol degrade substrates, generating peptides of varying length. (6) Large proteasomal products can be further cleaved in the cytosol by aminopeptidases such as TPPII. (7) Peptides with affinity for TAP will bind, and ATP-induced conformational changes in TAP will transport it through the ER membrane. (8) ERAP1 performs amino-terminal trimming in the ER. (9) These peptides may go directly into the PLC, or they may be retrotranslocated back into the cytosol through SEC61 and have to enter the ER again via TAP. (10) If the amino acid motif of the peptide matches the class I MHC molecule, it will then bind in the peptide groove, inducing a conformational change that stabilizes peptide binding. ERp57 will mediate the disulfide formation in $\alpha 2$, "locking" the peptide in. (11) If the correct conformational change is induced, all chaperone molecules will dissociate. (12) The trimer of class I heavy chain–β_2m–peptide is shuttled from the ER to the Golgi apparatus and subsequently to the plasma membrane of the cell.
(This figure also appears on page 20.)

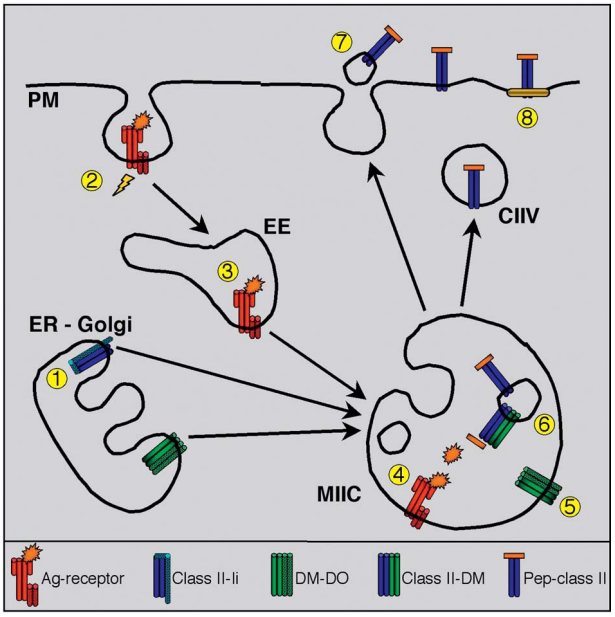


Figure 2.1 General pathway of exogenous antigen processing. Depicted is the general pathway of exogenous antigen processing and presentation. Numbered yellow circles indicate steps of the pathway at which variations can occur that will alter the hierarchy of peptide–class II complexes expressed by the APC (see text for details). (1) Relative levels of Ii isoforms (i.e., p31Ii vs. p41Ii, Section 2.2.1); (2) Effects of cell signaling (Sections 2.2.2 and 2.3); (3) Receptor-mediated antigen internalization and intracellular trafficking (Section 2.3); (4) Proteolytic processing of internalized antigen (Section 2.4.1); (5) Role of DM and DO in class II peptide loading (Section 2.4.2), (6) Intravesicular distribution of processing proteins (Section 2.4.2.4); (7) Exosomes and the cell-surface delivery of peptide–class II complexes (Section 2.4.3) (8) MHC class II signaling and partitioning of peptide–class II complexes into membrane microdomains (Section 2.4.3.2). PM: plasma membrane; EE: early endosome
(This figure also appears on page 32.).

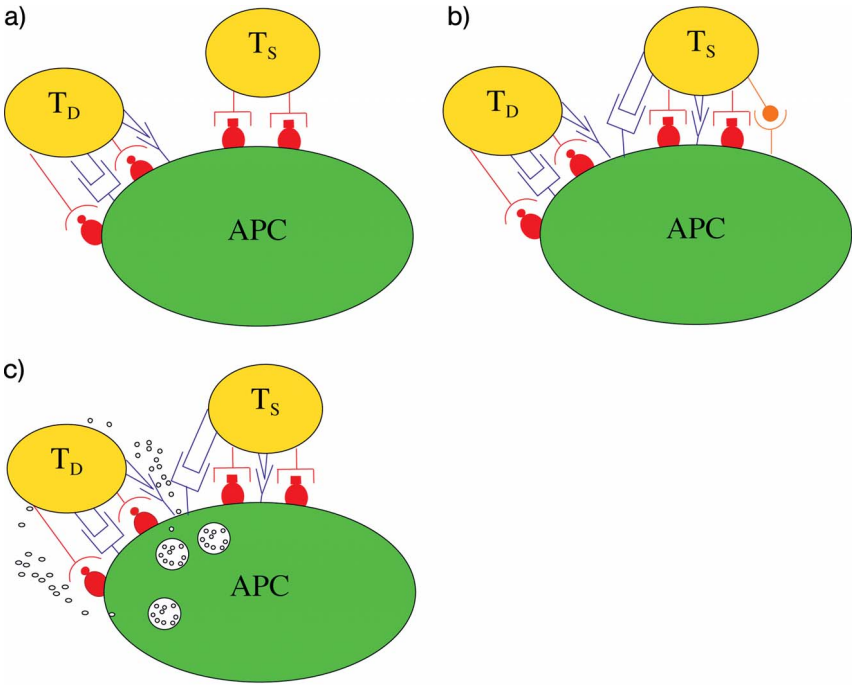


Figure 3.1 Possible mechanisms involved in immunodomination (a) Preemption of critical elements of the synapse by the dominant T cell. (b) Engagement of inhibitory receptors by the submissive T cell. (c) Lack of adequate directed secretion of APC factors. T_D = dominant T cell; T_S = submissive T cell TCR/MHC molecules are shown in red, costimulator ligands and receptors in blue, inhibitory receptors in orange, APC factors in white. (This figure also appears on page 20.)

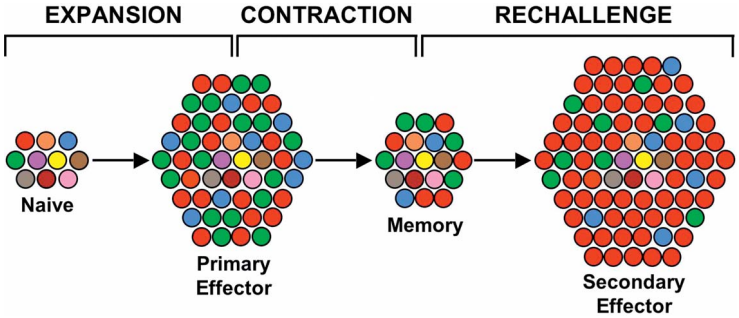


Figure 6.6 Shifts in repertoire and immunodominance following primary and secondary exposures to antigen. As primary immune responses are initiated, antigen-specific T cells become activated and expand in number. This results in a discernable shift in the T-cell repertoire as antigen-specific cells, indicated here in red, green, and blue, increase in frequency. A contraction phase ensues, following clearance of the inducing antigen; however, this downsizing is typically proportional. Consequently, the skewing of the repertoire and the hierarchy of immunodominance that develops during the expansion phase are imprinted on the memory pool. This phenomenon is sometimes referred to as immunological scarring. Although the repertoire and hierarchies of the primary effector and memory pools are usually similar, marked differences can arise following rechallenges. In this illustration, the red responders become most dominant. (This figure also appears on page 120.)

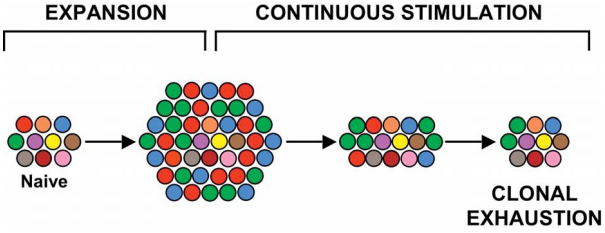


Figure 6.8 Continuous antigenic stimulation can drive responding CD8 T cells to deletion. Certain foreign antigens are not rapidly removed by the actions of the host's immune response. This is perhaps best exemplified by persistent viral infections. In these instances an initial response becomes detectable, resulting in repertoire shifts and the development of immunodominance. If the infection is not cleared by the overall immune response, then the responding cells may be subject to repetitive antigenic stimulation. Under these conditions certain clones and specificities of CD8 T cells may succumb to deletion, resulting in further changes in repertoire and epitope hierarchies. Notably, the deletion of CD8 T cells is exacerbated by the absence of CD4 T-cell help.
(This figure also appears on page 128.)

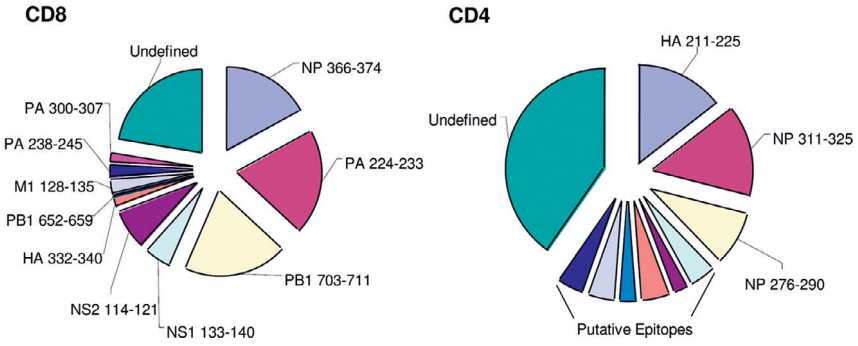
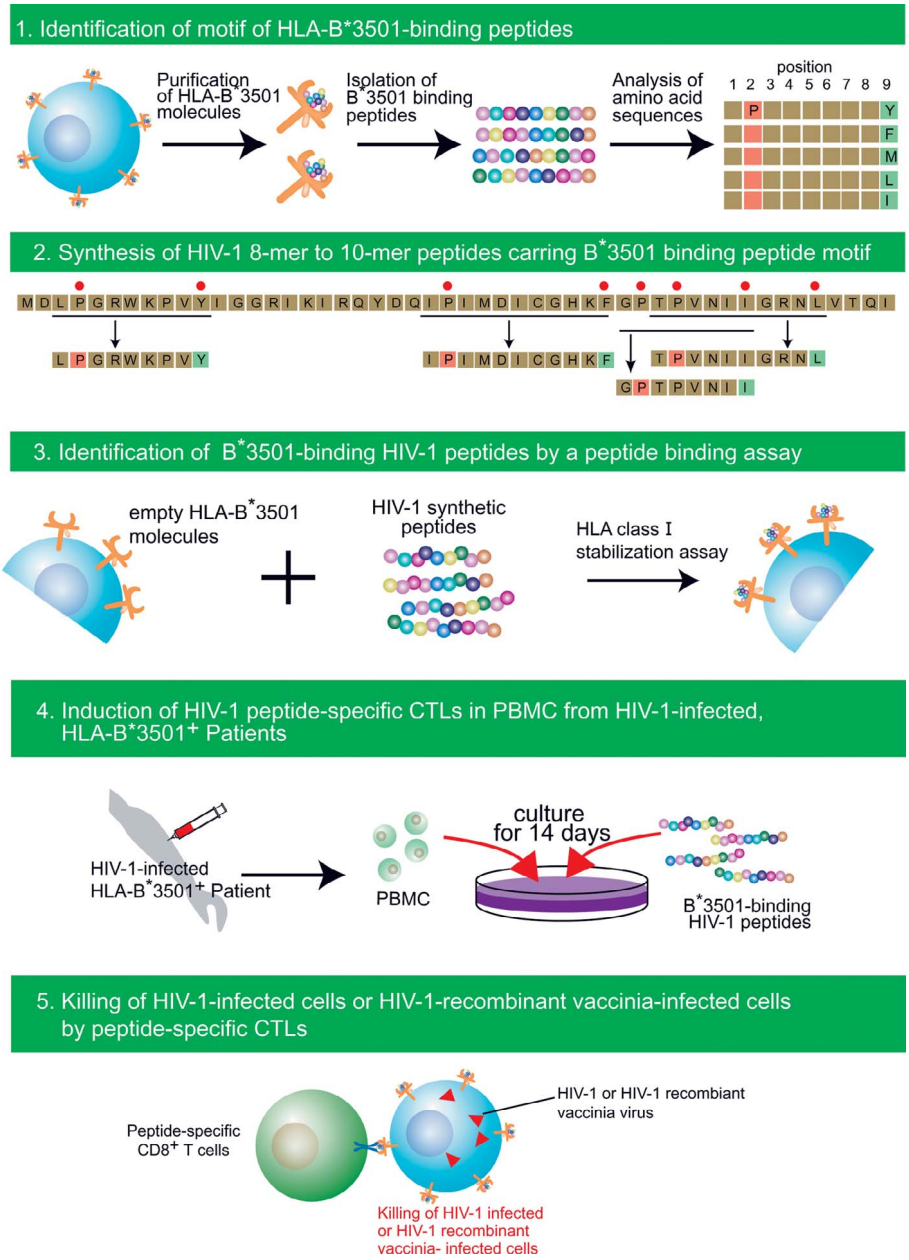


Figure 9.1 Antigen specificity in the lung airways following influenza virus infection. Three dominant epitopes and seven subdominant epitopes account for approximately 78% of the total $CD8^+$ T-cell response to influenza virus infection in the lung airways. The remaining 22% of the $CD8^+$ T-cell response is undetermined at this time. Two dominant and at least seven subdominant epitopes account for approximately 60% of the total $CD4^+$ T-cell response to influenza virus infection in the lung airways. The remaining 40% of the $CD4^+$ T-cell response is undetermined at this time. Some of the $CD4^+$ T-cell epitopes are listed as putative because detailed characterization of the epitopes has not yet been performed. (This figure also appears on page 192.)


1. Identification of motif of HLA-B*3501-binding peptides
Purification of HLA-B*3501 molecules
Isolation of B*3501 binding peptides
Analysis of amino acid sequences
position
1 2 3 4 5 6 7 8 9
2. Synthesis of HIV-1 8-mer to 10-mer peptides carrying B*3501 binding peptide motif
3. Identification of B*3501-binding HIV-1 peptides by a peptide binding assay
empty HLA-B*3501 molecules
HIV-1 synthetic peptides
HLA class I stabilization assay
4. Induction of HIV-1 peptide-specific CTLs in PBMC from HIV-1-infected, HLA-B*3501+ Patients
HIV-1-infected HLA-B*3501+ Patient
PBMC
culture for 14 days
B*3501-binding HIV-1 peptides
5. Killing of HIV-1-infected cells or HIV-1-recombinant vaccinia-infected cells by peptide-specific CTLs
Peptide-specific CD8+ T cells
HIV-1 or HIV-1 recombiant vaccinia virus
Killing of HIV-1 infected or HIV-1 recombinant vaccinia- infected cells

◀ **Figure 10.4** Identification of HLA-B*3501-restricted HIV-1 CTL epitopes by a method using reverse immunogenetics. (1) HLA-B*3501 molecules are isolated from HLA-negative cell lines transfected with the HLA-B*3501 gene. Peptides are eluted from isolated HLA-B*3501 molecules, and then the eluted peptides are sequenced to determine Immunodominant HIV-1 Epitopes Presented by HLA Allelesthe motif of HLA-B*3501-binding peptides. HLA-B*3501-binding peptide possessed Pro at position 2 and hydrophobic residues Tyr, Phe, Met, Leu, and Ile at the C-terminus. (2) 8-mer to 11-mer HIV-1 sequences carrying the HLA-B*3501 anchor residues at position 2 and the C-terminus are selected and synthesized. (3) Synthesized HIV-1 peptides are tested for binding to HLA-B*3501 by a peptide-binding assay such as the HLA class I stabilization assay. (4) HLA-B*3501-binding peptides are further used to induce peptide-specific CTLs from PBMCs of HLA-B*3501-positive, HIV-1-infected individuals. The PBMCs are stimulated with each HLA-B*3501-binding peptide or cocktails of the peptides. Peptide-stimulated PBMCs are cultured for approximately 14 days. Peptide-specific CTLs or $CD8^+$ T cells are identified by measuring the cytotoxic activity of cultured PBMCs toward peptide-pulsed cells or by measuring the production of IFN-γ by $CD8^+$ T cells in cultured PBMCs stimulated with peptide-pulsed cells. The peptides showing a positive response are considered epitope candidates. (5) To clarify whether the peptides are recognized as naturally occurring peptides by specific CTLs or $CD8^+$ T cells, cells infected with HIV-1 or HIV-1 recombinant vaccinia virus are used to stimulate IFN-γ production or for CTL activity. When peptide-specific T-cell clones or lines kill target cells infected with HIV-1 or HIV-1 recombinant vaccinia virus or produce IFN-γ after being stimulated with cells infected with HIV-1 or HIV-1 recombinant vaccinia virus, the peptides that these T cells recognize are concluded to be naturally occurring HIV-1 epitope peptides.
(This figure also appears on page 214.)

I
Mechanics of Antigen Processing