Immunodominance

The Choice of the Immune System

Edited by Jeffrey A. Frelinger
Immunodominance

Edited by
Jeffrey A. Frelinger
Related Titles

Frosch, M., Maiden, M. C. J. (Eds.)
**Handbook of Meningococcal Disease**
Infection Biology, Vaccination, Clinical Management
2006
ISBN 3-527-31260-9

Hamann, A., Engelhardt, B. (Eds.)
**Leukocyte Trafficking**
Molecular Mechanisms, Therapeutic Targets, and Methods
2005
ISBN 3-527-31228-5

Lutz, M., Romani, N., Steinkasserer, A. (Eds.)
**Handbook of Dendritic Cells**
Biology, Diseases and Therapies
2006
ISBN 3-527-31109-2

Kaufmann, S. H. E. (Ed.)
**Novel Vaccination Strategies**
2004
ISBN 3-527-30523-8

Meager, A. (Ed.)
**The Interferons**
Characterization and Application
2006
ISBN 3-527-31180-7

Kalden, J. R., Herrmann, M. (Eds.)
**Apoptosis and Autoimmunity**
From Mechanisms to Treatments
2003
ISBN 3-527-30442-8

Pollard, K. M. (Ed.)
**Autoantibodies and Autoimmunity**
Molecular Mechanisms in Health and Disease
2005
ISBN 3-527-31141-6

Kropshofer, H., Vogt, A.B. (Eds.)
**Antigen Presenting Cells**
From Mechanisms to Drug Development
2005
ISBN 3-527-31108-4
Immunodominance

The Choice of the Immune System

Edited by Jeffrey A. Frelinger
Shifts in repertoire and immunodominance following primary and secondary exposures to antigen. For further details see Figure 6.6 on page XXII.
Contents

Preface XIII

List of Contributors XV

Color Plates XIX

I Mechanics of Antigen Processing 1

1 Class I MHC Antigen Processing 3

Peter J. Miller and Edward J. Collins

1.1 Introduction 3
1.2 Properties of MHC 3
1.2.1 Structure of MHC 3
1.2.2 Polymorphic Residues Generate Specificity Pockets 5
1.3 Properties of Peptides 6
1.3.1 Peptides That Bind Are Not Random Sequences 6
1.3.2 Peptide-binding Motifs 6
1.3.3 Peptide Length Is Limited in Class I MHC Peptides 7
1.3.4 Binding Affinity 7
1.3.5 Molecular Recognition 9
1.3.6 Epitope Prediction 9
1.4 Cytosolic Processing 10
1.4.1 The Proteasome 10
1.4.2 The Immunoproteasome 12
1.4.3 Opening the Immunoproteasome 13
1.4.4 Peptide Trimming 14
1.4.5 Association of the Proteasome with the Endoplasmic Reticulum 15
1.5 Peptide Transport 15
1.5.1 Transport via TAP 16
1.5.2 TAP Selectivity 16
1.5.3 TAP-independent Peptide Transport 17
### Contents

1.5.3.1 Endogenous Peptides 17
1.5.3.2 Exogenous Peptides 18
1.6 Class I MHC Maturation and Peptide Loading 19
  1.6.1 ER Chaperones: Calnexin, Calreticulin, ERp57, and Tapasin 19
    1.6.1.1 Calnexin 19
    1.6.1.2 Tapasin 19
    1.6.1.3 ERp57 21
    1.6.1.4 Calreticulin 21
  1.6.2 Peptide Loading 21
1.7 Immunodominance and Class I MHC Peptide Processing 22

2 The Mechanics of Class II Processing: Establishment of a Peptide Class II Hierarchy 31
  James R. Drake and Andrea J. Sant

  2.1 General Overview 31
    2.1.1 Immunodominance and Crypticity 31
    2.1.2 The Impact of T-Cell Repertoire in the Experimental Analysis of Immunodominance 33
    2.1.3 Different Antigen-presenting Cells Have Different Functions 34
    2.1.4 The Phases of Antigen Processing 35
  2.2 Phase I: MHC Class II Biosynthesis and Delivery to Peptide-loading Compartments 36
    2.2.1 Invariant Chain Isoforms 36
    2.2.2 Effects of Cell Signaling on MHC Class II Transport 37
  2.3 Phase II: Antigen Internalization and Processing 38
    2.3.1 BCR-mediated Antigen Internalization 39
    2.3.2 Dendritic Cells and Macrophages 40
  2.4 Phase III: Formation and Expression of Antigenic Peptide by MHC Class II Molecules 41
    2.4.1 Proteolytic Antigen Processing 41
    2.4.2 Class II Peptide Loading 43
      2.4.2.1 DM 44
      2.4.2.2 DO 45
      2.4.2.3 DO-, DM-, and BCR-Mediated Antigen Processing 46
      2.4.2.4 The Distribution of MHC Class II and Other Proteins Within MIIC 46
    2.4.3 Cell-surface Delivery of Peptide–Class II Complexes 47
      2.4.3.1 Exosomes 48
      2.4.3.2 Signaling Properties of Peptide–Class II Complexes 49
  2.5 Conclusions 50
  Acknowledgments 50
3 The Phenomenon of Immunodomination: Speculations on the Nature of Immunodominance 57
Alessandro Sette and Roshni Sundaram

3.1 Introduction 57
3.2 MHC Binding, Cellular Processing, and T-Cell Repertoire are Major Determinants of Immunodominance 58
3.3 Previous Systematic Analysis of Immunodominance by Our Group 59
3.4 Cellular and Molecular Events in Immunodomination 62
3.5 Speculations on the Mechanism of Immunodomination 63
3.5.1 Involvement of APCs 63
3.5.2 Possible Involvement of the Immune Synapse in Immunodomination 65
3.5.3 The Potential Role of MTOC in Immunodomination 67
3.6 Significance of Studying Immunodominance for Vaccine Development 67
3.7 Conclusions 68

II Proteosome Specificity and Immuno-Proteosomes 73

4 Endogenous Antigen Processing 75
Jonathan W. Yewdell

4.1 Unbottling the Genie 75
4.2 DRiPs to the Rescue 76
4.3 The Ubiquitin–Proteasome Pathway 77
4.4 Pressing TDH Questions 80
4.4.1 Answer to Question 1 80
4.4.2 The Real World 81
4.4.3 Answer to Question 2 82
4.5 What Does This Have to Do With Immunodominance? 84

III Effect of the T Cell Repertoire on Dominance 89

5 Regulation of Early T-Cell Development in the Thymus 91
Thomas M. Schmitt and Juan Carlos Zúñiga-Pflücker

5.1 Introduction 91
5.2 T-Cell Development in the Thymus 92
5.2.1 Early T-Cell Progenitors 95
5.2.2 Thymocyte Migration 96
5.2.3 Factors Regulating T-cell Development 97
5.2.4 Notch and T-cell Development 98
6 CD8 T-cell Immunodominance, Repertoire, and Memory 109
Dalia E. Gaddis, Michael J. Fuller, and Allan J. Zajac

6.1 Introduction 109
6.2 CD8 T-Cell Responses and Memory 111
6.3 Analyzing the Memory Repertoire 114
6.4 Immunodominance 116
6.4.1 Antigen-related Factors 117
6.4.2 T Cell–related Factors 119
6.5 Epitope-dependent Skewing of the Repertoire During Primary, Memory, and Recall Responses 120
6.6 Heterologous Infections and Immunodominance 125
6.7 Chronic Infections and T-cell Heterogeneity 127
6.8 Repertoire Limitation and Immunodominance 131
6.9 Impact of Epitope Variation 133
6.10 Concluding Remarks 135

IV Effects of Pathogens on the Immune Response 147

7 Listeria monocytogenes Infection and the CD8+ T-Cell Hierarchy 149
Brandon B. Porter and John T. Harty

7.1 Introduction 149
7.2 Innate Immune Response to LM 150
7.3 Adaptive Immune Response to LM and Ag Presentation 151
7.4 Secreted Versus Non-secreted Ag 152
7.5 The Hierarchy of the CD8+ T-cell Responses to LM Epitopes 153
7.6 IFN-γ and the CD8+ T-cell Hierarchy 156
7.7 Timing of Ag Presentation and the CD8+ T-cell response 158
7.8 Conclusions 160
Acknowledgments 161

8 Immunodominance in Tuberculosis 163
David M. Lewinsohn and JoAnne L. Flynn

8.1 Immune Responses to Mycobacterium tuberculosis 163
8.2 B Cells 164
8.3 CD4 T Cells 164
8.4 CD8 T Cells 165
8.5 Antigen Processing and Presentation of Mtb Antigens 166
8.6 How Does Infection with Mtb Differ from Other Acute or Chronic Infections? 168
### 8.7 Immunodominance in the CD4 T-cell Response

- **8.7.1 Human** 169
- **8.7.2 Mouse** 170

### 8.8 Immunodominance in the CD8 T-cell Response

- **8.8.1 Human** 171
- **8.8.2 Mouse** 174

### 8.9 Non-classically Restricted T Cells in TB 176

### 8.10 Conclusions and Implications for Future Research 177

**Acknowledgments** 178

### 9 T-Cell Specificity and Respiratory Virus Infections 189

*Sherry R. Crowe and David L. Woodland*

- **9.1 Introduction** 189
- **9.2 Primary Immune Responses to Respiratory Virus Infections** 190
- **9.3 Specificity of the Primary Immune Response** 191
- **9.4 T-Cell Memory to Respiratory Virus Infections** 195
- **9.5 The Specificity of Memory T Cells** 197
- **9.6 Recall Responses to Secondary Infections** 198
- **9.7 Immunodominance Patterns in Recall Responses** 199
- **9.8 Modification of Immunodominance Hierarchies by Vaccination** 201
- **9.9 Conclusions** 202

**Acknowledgments** 203

### 10 Effects of Pathogens on the Immune Response: HIV 209

*Masafumi Takiguchi*

- **10.1 Introduction** 209
- **10.2 Identification of HIV-1 CTL Epitopes** 211
  - 10.2.1 Identification of HIV-1 CTL Epitopes by a Strategy Using Overlapping Peptides 212
  - 10.2.2 Identification of HIV-1 CTL Epitopes by the Strategy of Reverse Immunogenetics 215
- **10.3 Immunodominant HIV-1 Epitopes Presented by HLA Alleles Associated With Slow Progression to AIDS and Their Escape Mutants** 216
  - 10.3.1 HLA-B*57-restricted Immunodominant Epitopes and Their Escape Mutants 216
  - 10.3.2 HLA-B*27-restricted Immunodominant Epitopes 218
  - 10.3.3 HLA-B*51-restricted Immunodominant Epitopes 218
- **10.4 Immunodominant HIV-1 Epitopes Presented by HLA Alleles Associated With Rapid Progression to AIDS** 219
- **10.5 Immunodominant HIV-1 Epitopes Presented by Other HLA Alleles** 219
  - 10.5.1 HLA-A*02-restricted Immunodominant Epitopes 219
  - 10.5.2 HLA-B*08-restricted Immunodominant Epitopes 220
10.6 Escape Mutations and Viral Fitness 220
10.7 Effect of Nef-mediated HLA Class I Downregulation on Recognition of HIV-1-infected CD4+ T Cells by HIV-1-specific CD8+ T Cells 222
10.8 Skewed Maturation of HIV-1-specific CD8+ T Cells 224

11 The Effects of Pathogens on the Immune System: Viral Hepatitis 233
Mala Maini and Antonio Bertoletti

11.1 Introduction 233
11.2 The Viruses and the Disease 233
11.2.1 Genomic Organization 233
11.2.2 Prevalence 233
11.2.3 Hepatic Disease and Chronicity After Infection 235
11.3 Importance of CD4 and CD8 T Cells in HBV and HCV Control 235
11.4 Limitations of Existing Data 236
11.4.1 Low Frequency of HBV- and HCV-specific T Cells 237
11.4.2 Pre-selection of Epitopes 237
11.4.3 Stage of Infection 238
11.4.4 Variations in Viral Inoculum 238
11.5 Hierarchy of T-cell Responses During HBV Infection: Helper CD4 T-cell Response 238
11.6 Hierarchy of T-cell Responses During HBV Infection: Cytotoxic T-cell Response 240
11.7 Hierarchy of HCV Proteins 243
11.8 Hierarchy of HCV Epitopes 244
11.9 Immunodominance and Liver Pathology 248
11.10 Concluding Remarks 249

12 Immunodominance in the T-Cell Response to Herpesviruses 255
Michael W. Munks and Ann B. Hill

12.1 Introduction 255
12.2 General Considerations 256
12.2.1 Herpesviruses: A Brief Virological Primer 256
12.2.2 A General Framework for Thinking About Immunodominance in the T-Cell Response to Herpesvirus Infections 258
12.3 Immunodominance in the CD8 T-Cell Response to the Three Classes of Herpesvirus 260
12.3.1 Alphaherpesviruses 260
12.3.1.1 Human Studies: Immunodominance of Structural Virion Proteins that can be Presented in the Face of Immune Evasion 260
12.3.1.2 Mouse Studies of HSV 261
12.3.1.3 The Remarkable Immunodominance of gB-SSIEFARL in B6 Mice 262
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 fixes 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.