

Contents

Preface XV

List of Contributors XIX

List of Abbreviations XXIII

Color Plates XXVII

Part I Antigen Presentation in the Immune System 1

1 Some Old and Some New Findings on Antigen Processing and Presentation 3

Emil R. Unanue

- 1.1 Introduction 3
- 1.2 HEL Processing 4
- 1.3 Selection of Peptide Segments of HEL 9
- 1.4 HEL: Conformational Isomers 11
- 1.4.1 Biology of Type B T Cells 15
- 1.5 Negative Selection and Peripheral Activation to HEL Peptides 16
- 1.6 Response to HEL Immunization in the Draining Lymph Node 17

Part II Molecular Mechanisms of Antigen Processing 25

2 Antigen Entry Routes – Where Foreign Invaders Meet Antigen Presenting Cells 27

Percy A. Knolle

- 2.1 Introduction 27
- 2.2 Antigen Entry via the Gastrointestinal Tract 28
- 2.2.1 Peyer's Patches 29
- 2.2.2 Mesenteric Lymph Node 30
- 2.2.3 Dendritic Cells of the Lamina Propria 31
- 2.2.4 Pathogens Target Intestinal Antigen Presenting Cells 33

2.3	Antigen Entry via the Skin	35
2.4	Systemic Dissemination of Antigens/Infectious Microorganisms	38
2.5	Antigen Presenting Cells in the Liver	39
2.5.1	Dendritic Cells	39
2.5.2	Kupffer Cells	41
2.5.3	Liver Sinusoidal Endothelial Cells	42
2.6	Conclusion	44
3	Antigen Processing in the Context of MHC Class I Molecules	51
	<i>Frank Momburg</i>	<i>51</i>
3.1	Tracing the Needle in the Haystack: The Efficiency of Antigen Processing and Presentation by MHC Class I Molecules	51
3.2	The “Classical” Route: Loading of MHC Class I Molecules With Peptides Generated in the Cytoplasm	53
3.2.1	Cytosolic Peptide Processing by Proteasomes and other Proteases	53
3.2.1.1	Structure and Function of the Proteasomal Core and Interferon-induced Subunits	56
3.2.1.2	Targeting Proteins for ATP-dependent Degradation by 26S Proteasomes	56
3.2.1.3	Cleavage Properties of (Immuno)Proteasomes	57
3.2.1.4	Peptide Processing by Nonproteasomal Cytosolic Peptidases	59
3.3	Crossing the Border – Peptide Translocation into the ER by TAP	60
3.3.1	Structure and Function of TAP	60
3.3.2	Substrate Specificity of TAP	62
3.3.3	TAP-independent Peptide Entry into the ER	63
3.4	Fitting in the Best: TAP-associated Peptide Loading Complex Optimizes MHC-I Peptide Binding	63
3.4.1	Structure of MHC-I Molecules	64
3.4.2	Early Steps in the Maturation of MHC-I Molecules	64
3.4.3	Structure and Molecular Interactions of Tapasin	66
3.4.4	Optimization of Peptide Loading in the TAP-associated Loading Complex	67
3.5	On the Way Out: MHC-I Antigen Processing along the Secretory Route	70
3.6	Closing the Circle – Cross-presentation of Endocytosed Antigens by MHC-I Molecules	73
3.6.1	Phagosome-to-cytosol Pathway of MHC-I Peptide Loading	73
3.6.2	Endolysosomal Pathway of MHC-I Peptide Loading	76
4	Antigen Processing for MHC Class II	89
	<i>Anne B. Vogt, Corinne Ploix and Harald Kropshofer</i>	
4.1	Introduction	89
4.2	Types of Antigen Presenting Cells	90

4.2.1	Macrophages, B Lymphocytes and DCs	90
4.2.2	Tissue-resident APCs	91
4.2.3	Maturation State of APCs	92
4.2.3.1	Immature APCs	92
4.2.3.2	Mature APCs	92
4.3	Antigen Uptake by APCs	93
4.3.1	Macropinocytosis	93
4.3.2	Phagocytosis	94
4.3.3	Receptors for Endocytosis	95
4.4	Generation of Antigenic Peptides	97
4.4.1	Reduction of Disulfide Bonds: GILT	97
4.4.2	Regulation of the Proteolytic Milieu	98
4.4.3	Protease/MHC Interplay in Antigen Processing	99
4.5	Assembly of MHC II Molecules	102
4.5.1	Structural Requirements of MHC II	102
4.5.2	Biosynthesis of MHC II	103
4.5.3	Chaperones for Peptide Loading	104
4.5.3.1	HLA-DM/H2-DM	104
4.5.3.2	HLA-DO/H2-DO	107
4.6	Export of MHC II and Organization on the Cell Surface	109
4.6.1	Membrane Microdomains	109
4.6.2	Tubular Transport	112
4.7	Viral and Bacterial Interference	114
4.8	Concluding Remarks	116
5	Antigen Processing and Presentation by CD1 Family Proteins	129
	<i>Steven A. Porcelli and D. Branch Moody</i>	
5.1	Introduction	129
5.2	CD1 Genes and Classification of CD1 Proteins	129
5.3	Structure and Biosynthesis of CD1 Proteins	130
5.3.1	Three-dimensional (3D) Structures of CD1 Proteins	132
5.3.2	Molecular Features of CD1–Lipid Complexes	133
5.3.3	CD1 Pockets and Portals	135
5.4	Foreign Lipid Antigens Presented by Group 1 CD1	136
5.5	Self Lipid Antigens Presented by CD1	137
5.6	Group 2 CD1-restricted T Cells	138
5.6.1	Antigens Recognized by Group 2 CD1-restricted T Cells	139
5.7	Tissue Distribution of CD1 Proteins	140
5.8	Subcellular Distribution and Intracellular Trafficking of CD1	140
5.8.1	Trafficking and Localization of CD1a	141
5.8.2	Trafficking and Localization of CD1b	141
5.8.3	Trafficking and Localization of CD1c	143
5.8.4	Trafficking and Localization of CD1d	144
5.8.5	Trafficking and Localization of CD1e	145

5.9	Antigen Uptake, Processing and Loading in the CD1 Pathway	146
5.9.1	Cellular Uptake of CD1-presented Antigens	146
5.9.2	Endosomal Processing of CD1-presented Antigens	147
5.9.3	Accessory Molecules for Endosomal Lipid Loading of CD1	148
5.9.4	Non-endosomal Loading of Lipids onto CD1 Molecules	149
5.10	Conclusions	150

Part III Antigen Presenting Cells' Ligands Recognized by T- and Toll-like Receptors 157

6	Naturally Processed Self-peptides of MHC Molecules	159
	<i>Harald Kropshofer and Sebastian Spindeldreher</i>	
6.1	Introduction	159
6.2	Milestone Events	160
6.2.1	Nomenclature	160
6.2.1.1	Autologous Peptides	160
6.2.1.2	Endogenous Peptides	161
6.2.1.3	Natural Peptides Ex Vivo and In Vitro	161
6.2.2	Extra Electron Density Associated to MHC Molecules	162
6.2.3	Acidic Peptide Elution Approach	163
6.2.4	First Natural Foreign Peptides on MHC Class II	165
6.2.5	First Natural Viral Epitopes on MHC Class I	165
6.2.6	Self-peptide Sequencing on MHC Class I: the First Anchor Motifs	166
6.2.7	First Murine MHC Class II-associated Self-peptides: Nested Sets	167
6.2.8	First Human MHC Class II-bound Self-peptides: Hydrophobic Motifs	169
6.3	Progress in Sequence Analysis of Natural Peptides	172
6.3.1	Edman Microsequencing	172
6.3.2	Electrospray Ionization Tandem Mass Spectrometry	173
6.3.3	Automated Tandem Mass Spectrometry	175
6.3.4	MAPPs: MHC-associated Peptide Proteomics	176
6.4	Natural Class II MHC-associated Peptides from Different Tissues and Cell-types	177
6.4.1	Peripheral Blood Mononuclear Cells	177
6.4.2	Myeloid Dendritic Cells	178
6.4.3	Medullary Thymic Epithelial Cells	179
6.4.4	Splenic APCs	181
6.4.5	Tumor Cells	181
6.4.6	Autoimmunity-related Epithelial Cells	182
6.5	The CLIP Story	183
6.5.1	CLIP in APCs Lacking HLA-DM	184
6.5.2	Flanking Residues and Self-release of CLIP	184
6.5.3	CLIP in Tetraspan Microdomains	185

6.5.4	CLIP as an Antagonist of T _H 1 Cells	188
6.6	Outlook: Natural Peptides as Diagnostic or Therapeutic Tools	189
7	Target Cell Contributions to Cytotoxic T Cell Sensitivity	199
	<i>Tatiana Lebdeva, Michael L. Dustin and Yuri Sykulev</i>	<i>199</i>
7.1	Introduction	199
7.2	Intercellular Adhesion Molecule 1 (ICAM-1)	200
7.2.1	Adhesion Molecules on the Surface of APC and Target Cells	200
7.2.2	ICAM-1 Structure and Topology on the Cell Surface	200
7.2.3	ICAM-1 as Co-stimulatory Ligand and Receptor	201
7.2.4	ICAM-1-mediated Signaling	203
7.2.5	Role of ICAM-1 in Endothelial Response to Leukocytes	206
7.2.6	ICAM-1 Association with Lipid Rafts	206
7.3	Major Histocompatibility Complex (MHC)	208
7.3.1	MHC Molecules	208
7.3.2	Molecular Associations of MHC-I Molecules	208
7.3.3	Association of MHC-I and ICAM-1	211
7.3.4	Could APC and Target Cells Play an Active Role in Ag Presentation?	212
7.3.5	Identical pMHCs are Clustered in the Same Microdomain	212
7.3.6	Identical pMHC can be Recruited to the Same Microdomain During Target Cell–T Cell Interaction	213
7.3.7	Co-clustering of MHC and Accessory Molecules	213
7.3.8	Role of Cytoskeleton	214
7.4	Conclusion	215
8	Stimulation of Antigen Presenting Cells: from Classical Adjuvants to Toll-like Receptor (TLR) Ligands	221
	<i>Martin F. Bachmann and Annette Oxenius</i>	
8.1	Synopsis	221
8.2	Pathogen-associated Features that Drive Efficient Immune Responses	221
8.3	Composition and Function of Adjuvants	222
8.4	TLR Protein Family in Mammals	224
8.4.1	TLR4	226
8.4.2	TLR2	227
8.4.3	TLR5	227
8.4.4	TLR11	228
8.4.5	TLR12 and TLR13	228
8.4.6	Nucleic Acids as PAMPs	228
8.4.6.1	TLR3	228
8.4.6.2	TLR7 and TLR8	229
8.4.6.3	TLR9	229

8.4.7	Compartmentalization of Sensing Renders the Nucleic Acid PAMPs	229
8.5	TLR Signaling	230
8.5.1	Signal Transduction Across the Membrane	231
8.5.2	MyD88-dependent Pathways	231
8.5.3	MyD88-independent Pathways	232
8.6	TLR-independent Recognition of PAMPs: Nods, PKR and Dectin-1	233
8.6.1	Nods	233
8.6.2	PKR (IFN-inducible dsRNA-dependent Protein Kinase)	234
8.6.3	Dectin-1	234
8.7	Therapeutic Potential of TLRs and their Ligands	235
8.8	Conclusion	237
Part IV	The Repertoire of Antigen Presenting Cells	245
9	Evolution and Diversity of Macrophages	247
	<i>Nicholas S. Stoy</i>	
9.1	Evolution of Macrophages: Immunity without Antigen Presentation	247
9.1.1	Introduction	247
9.1.2	<i>Drosophila</i> : a Window into Innate Immunity	247
9.1.3	Evolution of Adaptive Immunity: Macrophages in a New Context	255
9.2	Diversity of Macrophages in Mammalian Tissues	257
9.2.1	Classifying Heterogeneity	257
9.2.2	Phenotypic Manipulations and Transdifferentiations: Routes to and from Macrophages	258
9.2.3	Function-related 'Markers' in Macrophages and DCs	262
9.2.4	Macrophage Phenotypic Diversity in Response to Microbial Challenge	266
9.2.5	Interactions between Tissue Microenvironments and Macrophages Generate Diversity	283
9.2.6	Sequential and Regulatory Changes in Macrophage Phenotypes: Limiting Pro- and Antiinflammatory Responses	292
9.2.6.1	Pre-TLR and TLR Regulation of Immune Responses	293
9.2.6.2	Signal Transduction in the Regulation of Immune Responses	294
9.2.6.3	Regulation of Immune Responses by Cytokines and other Bioactive Molecules	299
9.2.6.4	Regulation of Immune Responses by Decoys	300
9.2.6.5	Regulation of Immune Responses by the Adaptive Immune System	300
9.2.6.6	Regulation of Immune Responses by Apoptosis	301

- 9.2.6.7 Interaction of Regulatory Mechanisms during Immune Responses 301
- 9.2.7 Macrophage Diversity: an Overview 302
- 10 Macrophages – Balancing Tolerance and Immunity 331**
Nicholas S. Stoy 331
- 10.1 Balancing Tolerance and Immunity 331
- 10.1.1 Introduction 331
- 10.1.2 Macrophage Phenotypes: Effects on Immunity and Tolerance 332
- 10.1.3 Concept of Innate (Peripheral) Tolerance 334
- 10.1.4 Concept of Adaptive Tolerance 335
- 10.1.5 Innate Tolerance: Receptors, Responses and Mechanisms 342
- 10.1.6 Incorporating NK and NT Cells into the Innate Tolerance/Innate Immunity Paradigm 349
- 10.1.7 Definitions and Terminology 354
- 10.2 Ramifications of the Paradigm: Asthma 356
- 10.3 Ramifications of the Paradigm: Autoimmunity 362
- 10.4 Summary and Conclusions: Towards Immune System Modeling and Therapeutics 378
- 11 Polymorphonuclear Neutrophils as Antigen-presenting Cells 415**
Amit R. Ashtekar and Bhaskar Saha
- 11.1 Introduction 415
- 11.2 PMN as Antigen-presenting Cells 417
- 11.2.1 Basic Criteria of an APC for T Cells 417
- 11.2.2 Acquisition of Antigens 418
- 11.2.3 Antigen Processing 420
- 11.2.4 Expression of MHC Class I/II and Co-stimulatory Molecules 424
- 11.2.5 Delivery of Second Signal 427
- 11.2.6 Alteration in Cytokine Milieu 430
- 11.3 Evolution of Newer Thoughts as PMN March to a Newer Horizon 434
- 12 Microglia – The Professional Antigen-presenting Cells of the CNS? 441**
Monica J. Carson
- 12.1 Introduction: Microglia and CNS Immune Privilege 441
- 12.1.1 What are Microglia? 441
- 12.1.2 Is Immune Privilege Equivalent to Immune Isolation? 442
- 12.2 Do Microglia Differ from Other Macrophage Populations? 444
- 12.2.1 Microglia are Likely of Mesodermal Origin 444
- 12.2.2 Parenchymal Microglia are not the only Myeloid Cells in the CNS 444
- 12.2.3 In Contrast to other Macrophages, Parenchymal Microglia are not Readily Replaced by Bone Marrow Stem Cells 444

12.2.4 Microglia Display Stable Differences in Gene Expression that Distinguish them from Other Macrophage Populations 446

12.2.5 Morphology is not a Reliable Parameter to Differentiate Microglia from Other Macrophage Populations 447

12.3 To What Extent is Microglial Phenotype Determined by the CNS Microenvironment? 448

12.4 Microglia versus Macrophages/Dendritic Cells as Professional Antigen-presenting Cells 449

12.4.1 In vitro and Ex Vivo Assays of Antigen-presentation 449

12.4.2 Culture Conditions can have Profound Effects on Microglia Effector Functions as Assayed In Vitro 450

12.4.3 In Vivo Assays of Antigen-presentation 451

12.4.4 Antigen-presentation by Microglia is Necessary to Evoke or Sustain Neuroprotective T Cell Effector Function 451

12.4.5 Why were Microglia Unable to Initiate Protective T Cell Responses? 453

12.5 TREM-2 Positive Microglia may Represent Subsets Predisposed to Differentiate into Effective Antigen-presenting Cells 454

12.6 Are Microglia the “Professional Antigen-presenting Cell of the CNS?” 456

13 Contribution of B Cells to Autoimmune Pathogenesis 461

Thomas Dörner and Peter E. Lipsky

13.1 Introduction 461

13.2 Autoimmunity and Immune Deficiency 463

13.2.1 Basic Mechanisms Providing Diversity to the B Cell Receptor 463

13.2.2 Ig V Gene Usage by B Cells of Healthy Individuals 465

13.2.3 Potential Abnormalities in Molecular Mechanisms Underlying IgV Gene Usage in Systemic Autoimmune Diseases 465

13.2.4 Lack of Molecular Differences in V(D)J Recombination in Patients with Systemic Autoimmune Diseases 466

13.2.5 Receptor Editing/Revision and Autoimmunity 467

13.2.6 Selective Influences Shaping the Ig V Gene Repertoire in Autoimmune Diseases 469

13.2.6.1 IgV Gene Usage by Autoantibodies 469

13.2.7 Role of Somatic Hypermutation in Generating Autoantibodies 470

13.3 Disturbed Homeostasis of Peripheral B Cells in Autoimmune Diseases 472

13.4 Signal Transduction Pathways in B Cells 473

13.4.1 B Cell Function Results from Balanced Agonistic and Antagonistic Signals 474

13.4.1.1 Altered B Cell Longevity can Lead to Autoimmunity 474

13.4.1.2 Altered B Cell Activation can Lead to Autoimmunity 476

13.4.1.3 Inhibitory Receptors of B Cells 477

- 13.4.1.4 Inhibitory Receptor Pathways and Autoimmunity 480
- 13.5 B Cell Abnormalities Leading to Rheumatoid Arthritis 482
- 13.5.1 Activated B Cells may Bridge the Innate and Adaptive Immune System 483
- 13.5.2 “Humoral Imprinting” in Rheumatoid Arthritis 484
- 13.5.3 Indications of Enhanced B Cell Activity in RA 485
- 13.5.4 T Cell Independent B Cell Activation 486
- 13.6 Depleting anti-B Cell Therapy as a Novel Therapeutic Strategy 487

14 Dendritic Cells (DCs) in Immunity and Maintenance of Tolerance 503

Magali de Heusch, Guillaume Oldenhove and Muriel Moser

- 14.1 Introduction 503
- 14.2 Dendritic Family 503
- 14.3 DCs at Various Stages of Maturation 504
- 14.4 Immature DCs 505
- 14.5 Homing of DCs into Secondary Lymphoid Organs 505
- 14.6 DCs as Adjuvants 507
- 14.7 DC Subsets 508
- 14.7.1 Classical DCs 508
- 14.7.2 Plasmacytoid DCs 508
- 14.8 DCs in T Cell Polarization 509
- 14.9 Tolerogenic DC 510
- 14.10 Mechanisms of Tolerance 512
- 14.10.1 Lack of Co-stimulation 512
- 14.10.2 Peripheral Deletion of Autoreactive T Cells 512
- 14.10.3 Dynamics of Cellular Contacts 512
- 14.10.4 Induction of Regulatory T Cells 513
- 14.11 CD28-B7 Bidirectional Signaling 514
- 14.12 Crosspriming 515
- 14.13 Cross-presentation and Cross-tolerization 515
- 14.14 DC as Regulators of T Cell Recirculation 516
- 14.15 DC-based Immunotherapy of Cancer 517
- 14.16 Conclusion 517

15 Thymic Dendritic Cells 523

Kenneth Shortman and Li Wu

- 15.1 Thymic Dendritic Cells 523
- 15.2 Localisation and Isolation of Thymic DC 523
- 15.3 Pickup of Antigens by Thymic DC 524
- 15.4 Subtypes of Thymic DC 525
- 15.5 Major Thymic cDC Population 525
- 15.6 Minor Thymic cDC Population 526
- 15.7 Thymic pDC 527
- 15.8 Maturation State and Antigen Processing Capacity of Thymic DC 527

XIV | Contents

- 15.9 Cytokine Production by Thymic DC 528
- 15.10 DC of the Human Thymus 529
- 15.11 Turnover Rate and Lifespan of the Thymic DC 530
- 15.12 Endogenous versus Exogenous Sources of Thymic DC 530
- 15.13 Lineage Relationship and Differentiation Pathways of Thymic cDC 531
- 15.14 Lineage Relationships and Developmental Pathways of Thymic pDC 532
- 15.15 Thymic cDC do not Mediate Positive Selection 533
- 15.16 Thymic cDC and Negative Selection 533
- 15.17 Role of pDC in the Thymus 535

Part V Antigen Presenting Cell-based Drug Development 539

16 Antigen Presenting Cells as Drug Targets 541

Siquan Sun, Robin Thurmond and Lars Karlsson

- 16.1 Introduction 541
- 16.2 Roles of DC in disease 542
 - 16.2.1 Transplantation 542
 - 16.2.2 Autoimmune Diseases 542
 - 16.2.3 Allergy/Asthma 543
 - 16.2.4 Cancer 543
- 16.3 Marketed Drugs Affecting APC function 544
- 16.4 New Potential APC Drug Targets 547
 - 16.4.1 APC Activation 547
 - 16.4.2 Antigen Presentation 550
 - 16.4.3 Co-stimulation 553
 - 16.4.4 Cell Adhesion 555
 - 16.4.5 APC Chemotaxis 557
 - 16.4.6 APC Survival 558
 - 16.4.7 Intracellular Signaling 559
 - 16.4.8 APC Depletion 560
- 16.5 APC per se as Drugs – DC-based Immunotherapy Therapy 561
 - 16.5.1 DC-based Cancer Vaccines 561
 - 16.5.2 Targeting and Activating DC In Vivo 562
 - 16.5.3 DC-based Immunotherapy for Transplantation and Autoimmune Diseases 563
- 16.6 Conclusion 564

Glossary 585

Index 599