Contents

Volume 1

2.1

	Preface V		
	List of Contributors XXXIX		
Part A	Dendritic Cell Biology 1		
1	Introduction to Some of the Issues and Mysteries Considered in this		
	Book on Dendritic Cells 3		
	Ralph M. Steinman		
1.1	Dendritic Cells as a Distinct Hematopoietic Lineage 3		
1.1.1	Chapters 1–16, the Life History of Dendritic Cells 3		
1.1.2	Questions Concerning the Dendritic Cell Lineage 4		
1.2	Control of Lymphocyte Responses by Dendritic Cells 4		
1.2.1	Chapters 17–30, Initiation of Immunity 4		
1.2.2	Questions Concerning Antigen Uptake, Processing and		
	Presentation 5		
1.2.3	Questions Concerning Dendritic Cell Maturation 5		
1.3	Dendritic Cells in Disease Pathogenesis 6		
1.3.1	Chapters 31–51, Dendritic Cells in Infectious and Other Diseases 6		
1.3.2	Some Questions on the Roles of Dendritic Cells in Diseases 7		
1.4	Dendritic Cells and the Design of Vaccines and New Therapies 7		
1.4.1	Chapters 52-55, Dendritic Cells in Immunotherapy 7		
1.4.2	Dendritic Cells and the Design of Vaccines against Infectious		
	Diseases 8		
	References 9		
ı	Dendritic Cell Development 13		
2	Bone Marrow Progenitors of Dendritic and Natural Interferon-producing Cells 13		
	Markus G. Manz		

Hematopoietic Stem Cells and Successive Lineage-restricted Early

Handbook of Dendritic Cells. Biology, Diseases, and Therapies. Edited by M. B. Lutz, N. Romani, and A. Steinkasserer. Copyright © 2006 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim ISBN: 3-527-31109-2

Hematopoietic Progenitor Cells

Contents	
2.2	Proposed Models for Dendritic and Natural Interferon-producing Cell Differentiation 15
2.3	Unexpected Redundancy in Dendritic and Natural Interferon- producing Cell Development from both Lymphoid and Myeloid Restricted Hematopoietic Progenitor Cells 16
2.4	Immediate Dendritic and Natural Interferon-producing Cell Precursors 17
2.5	Proposed "flt3-license" Working Model for Steady-State Dendritic and Natural Interferon-producing Cell Development from Early Hematopoietic Progenitor Cells 18
2.6	Conclusions 20
	Acknowledgement 21
	References 21
2	Growth Factors 27
3	Herbert Strobl, Barbara Platzer, Almut Jörgl, Sabine Taschner,
	Leonhard Heinz and Peter Reisner
3.1	Introduction 27
3.2	Short Description of Key Cytokines Involved in DC Development 28
3.2.1	Flt3 Ligand (FLT3L, FL) 28
3.2.2	GM-CSF (Granulocyte-macrophage Colony-stimulating Factor) 29
3.2.3	Interleukin 3 (IL-3) 30
3.2.4	Interleukin 4 (IL-4) 30
3.2.5	Interleukin-15 (IL-15) 31
3.2.6	TNFα (Tumor Necrosis Factor-alpha) 31
3.2.7	TGF-β1 (Transforming Growth Factor Beta-1) 32
3.3	Regulation of <i>in vitro</i> DC Hematopoiesis by Cooperating Cytokine Signals 33
3.3.1	Cytokines in the Induction and Amplification of CD1a ⁺ Myeloid DC Subsets from Hematopoietic Progenitor Cells <i>in vitro</i> 33
3.3.2	Cytokines for Pre-expansion of Myeloid DC Progenitor Cells 35
3.3.3	Cytokine Combinations that Promote Myeloid DC Expansion
	Reciprocally Inhibit Plasmacytoid DC Development in Suspension
2.2.4	Cultures 36
3.3.4	TGF-β1 and its Essential Co-signals for LC Differentiation from
225	Hematopoietic Progenitor/Stem Cells 39 TGF-β1 Induces LC Differentiation from Monocyte Intermediates 40
3.3.5	Redundancy among Cytokine Signals Directing LC Differentiation
3.3.6	from CD34 ⁺ Hematopoietic Progenitor Cells 41
3.3.7	TGF-β1-dependent LC Induction by <i>in vivo</i> Occurring Candidate
3.3.7	Precursors 41
3.3.8	Cytokines Promoting the Generation of Monocyte-derived DC 42
3.3.9	Evidence for Cellular Heterogeneity of DC Arising from CD34 ⁺
	Progenitors or Monocytes 43
3.4	Conclusions 43
	References 44

4	Transcription Factors: Deciphering the Transcription Factor Network of Dendritic Cell Development 53
	Thomas Hieronymus and Martin Zenke
4.1	Introduction 53
4.2	Ikaros 54
4.3	RelB 55
4.4	PU.1 56
4.5	C/EBPa 57
4.6	Pax5 60
4.7	IRF family 60
4.8	Id2 63
4.9	Runx3 64
4.10	Gfi1 64
4.11	Concluding Remarks 65
	References 66
П	Sentinel Dendritic Cells in Nonlymphoid Organs 73
"	Sentine Denuritic Cens in Nonlymphold Organs 75
5	Epidermal Langerhans Cells 73
	Nikolaus Romani, Christoph H. Tripp, Gudrun Ratzinger,
	Christine Heufler, Franz Koch, Sem Saeland and Patrizia Stoitzner
5.1	Introduction and Definition 73
5.2	A Short Review of the History of Langerhans Cells 73
5.3	Characterization and Morphology of Langerhans Cells 75
5.4	Entry of Langerhans Cells into the Epidermis in Ontogeny and
	Adulthood 76
5.4.1	Entry of Langerhans Cells into the Epidermis during Ontogeny 76
5.4.2	Entry and Turnover of Langerhans Cells into the Adult Epidermis under Homeostatic Conditions 77
5.4.3	Entry and Turnover of Langerhans Cells into the Adult Epidermis under Inflammatory Conditions 78
5.5	Lineage of Langerhans Cells 79
5.6	Langerhans Cells in Lymphoid Organs 80
5.7	Langerhans Cells as a Paradigm for Dendritic Cell Function 82
5.8	The Changing of the Paradigm 84
5.9	Can Langerhans Cells Induce Immunity in vivo? 85
5.10	Can Langerhans Cells maintain Peripheral Tolerance in vivo? 86
5.11	Can Langerhans Cells be Applied in Immunotherapy? 88
5.12	Recent Methodical Advances Relevant for the Study of Langerhans Cells 89
	Acknowledgements 90
	References 90

x	Contents
---	----------

6	Characterization of Dendritic Cells and other Antigen-presenting Cells in the Eye 101		
	Joan Stein-Streilein		
6.1	Introduction 101		
6.2	APC in Various Regions of the Eye 103		
6.3	DC/APC in the Retina 103		
6.4	DC/APC in the Cornea 105		
6.5	DC/APC in the Anterior Chamber 105		
6.6	Mechanisms of ACAID Induction in the Spleen 107		
6.7	The Role of the F4/80 Protein in ACAID 109		
6.8	Therapeutic Potential of ACAID APC 110		
6.9	Conclusions and Implications 111		
	Acknowledgements 111		
	Abbreviations 112		
	References 112		
7	Toll-like Receptors 119		
	Hubertus Hochrein and Hermann Wagner		
7.1	TLR and their Ligands 119		
7.2	TLR Subfamilies 121		
7.3	TLR and Dendritic Cell Subsets 122		
7.4	TLR Signaling 123		
7.5	What Determines the Outcome of the Immune Responses? 124		
	References 126		
8	C-type Lectins on Dendritic Cells: Antigen Receptors and Modulators of		
	Immune Responses 129		
	Yvette van Kooyk and Teunis B.H. Geijtenbeek		
8.1	Introduction 129		
8.2	DCs and Antigen Recognition Receptors 130		
8.3	CLRs as Antigen Receptors for Homeostatic Control 130		
8.4	CLRs as Adhesion Receptors 131		
8.5	CLRs as Pathogen Receptors 133		
8.5.1	HIV-1 as Prototypic Example for Virus-DC-SIGN Interactions 133		
8.6	Glycan Modifications and Pathogen Recognition by DCs 134		
8.7	CLRs as Signaling Receptors 136		
8.8	CLRs and Recognition of Cancer 137		
8.9	Concluding Remarks 137		
	Abbreviations 138		
	Acknowledgements 138		
	References 139		

9	Scavenger Receptors on Dendritic Cells 141 Emma J. McKenzie, Subhankar Mukhopadhyay, Siamon Gordon and
	Luisa Martinez-Pomares
9.1	Introduction 141
9.2	Structure and Binding Properties of Mammalian Scavenger
7.2	Receptors 142
9.2.1	Class A Scavenger Receptors 143
9.2.1.1	SR-A I,II and III (SR-A) 143
9.2.1.2	MARCO 144
9.2.1.3	SRCL-I 146
9.2.2	CD36 147
9.2.3	LOX-1 148
9.2.4	SREC-I 149
9.2.5	Other Members of the SR Family 149
9.2.5.1	CD68 149
9.2.5.2	SR-B1, FEEL-1 and FEEL-2 150
9.3	Role of Scavenger Receptors in Dendritic Cell Biology 150
9.3.1	SR and Antigen Internalization for Presentation to the Acquired
	Immune System 151
9.3.1.1	In vitro Generation of SR Ligands and its Effect in
	Immunogenicity 151
9.3.1.2	Crosspresentation of Ag Through Uptake of Apoptotic Cells 152
9.3.1.3	Crosspresentation of Ag Acquired through Live Cell Nibbling 153
9.3.1.4	Crosspresentation of Peptide-chaperone Complexes 153
9.3.2	Role of SR in the Modulation of Dendritic Cell Activation 155
9.3.2.1	Role of SR in Modulation of Dendritic Cell Phenotype in Response to Uptake of Apoptotic Cells 155
9.3.2.2	Role of SR in Modulation of Dendritic Cell Phenotype in Response to
).J.L.L	Uptake of Necrotic Cells 155
9.3.2.3	Cross-talk between SR and Toll-like Receptors 156
9.4	Concluding Remarks 156
	References 157
10	Production of the Long Pentraxin PTX3 by Myeloid Dendritic Cells:
	Linking Cellular and Humoral Innate Immunity 165
	Paola Allavena, Barbara Bottazzi, Andrea Doni, Luigina Romani,
	Cecilia Garlanda and Alberto Mantovani
10.1	Introduction 165
10.1	The Pentraxin Superfamily and the Prototypic Long PTX3: Molecules
10.2	and Ligands 165
10.3	Myeloid DC as a Major Source of PTX3: Regulation of
10.5	Production 168
10.4	Blood-circulating Myeloid, but not Plasmacytoid,
	DC Produce PTX3 169
10.5	Role of PTX3 in Innate Immunity 170

ХII	Contents				
•	10.6	Function of Antigen Presenting Cells in PTX3-deficient Mice 170			
	10.7	Conclusion 171			
		References 172			
	13	Gene Profiling of Dendritic cells during Host-Pathogen			
		Interactions 175			
		Maria Foti, Francesca Granucci, Mattia Pelizzola, Norman Pavelka,			
	Ottavio Beretta, Caterina Vizzardelli, Matteo Urbano, Ivan Zanoni,				
		Giusy Capuano, Francesca Mingozzi, François Trottein, Toni Aebischer and Paola Ricciardi-Castagnoli			
	11.1	Dendritic Cells as Sentinels of the Immune System: Tissue-resident			
		DC and Migratory DC 175			
	11.2	Study of the Complexity of the Immune System using Gene			
		Profiling 177			
	11.3	Discovery of IL2 Production by DC using Global Technologies and the			
		NK-DC Interplay 179			
	11.4	Profiling of Pathogens and Cells of the Innate Response: Mucosal			
		Epithelial Cells, Phagocytic Cells (Neutrophils and Macrophages) 180			
	11.5	Dendritic Cells and Pathogen Interaction: Dendritic Cells as a Link			
		between Innate and Acquired Immunity 182			
	11.6	Dendritic Cells as Sensors of Infection 184			
	11.7	DC Transcriptional Profile Induced by Pathogen Teaches the Dynamic			
		of the Interactions: DC Transcriptome; Core and Specific			
		Responses 185			
	11.8	DC and Shistosoma Mansoni Specific Signature 186			
	11.9	DC and Leishmania Mexicana: Molecular Profile of the			
	11 10	Interaction 190			
	11.10	Conclusions 192			
	References 192				
	III Dendritic Cells in Secondary Lymphoid Organs 199				
	12 Dendritic Cell Subtypes 199				
		Ken Shortman and Jóse A. Villadangos			
	12.1	Introduction 199			
	12.2	DC Surface Antigen Heterogeneity and the Recognition of DC			
		Subtypes 201			
	12.3	DC Subtypes in Steady-state versus Infected Mice 202			
	12.4	Extraction and Enrichment of DC from Lymphoid Tissue 203			
	12.5	Plasmacytoid versus Conventional DC 203			
	12.6	Spleen DC Subtypes 204			
	12.7	Lymph Node DC Subtypes 206			
	12.8	Thymic DC 208			
	12.9	The Maturation State of Lymphoid Organ DC Subtypes 209			
	12.10	Generation and Lifespan of DC Subtypes 210			

12.11 12.12	Human DC Subtypes 211 Functional Differences between DC Subtypes 212 References 212
IV	Circulating Dendritic Cells and their Precursors 219
13	pDC: From Plasmacytoid Dendritic Cell Precursors to Professional Type 1 Interferon-producing Cells 219 Yong-Jun Liu, Holger Kanzler, Yui-Hsi Wang, Yi-Hong Wang, Michel Gilliet, Wei Cao and Tomoki Ito
13.1	Introduction 219
13.1.1	A Mysterious Cell Type with Plasmacytoid Morphology 219
13.1.2	A Mysterious Cell Type that has the Capacity to Produce Huge Amounts of Type 1 IFNs 221
13.1.3	From pDC to IPC 221
13.1.4	pDCs/IPCs in Mice, Rat, Pig, and Monkey 222
13.2	Isolation and Characterization of pDCs/IPCs 222
13.2.1	Isolation of Human pDCs/IPCs 222
13.2.2	Isolation of Mouse pDCs/IPCs 222
13.2.3	pDC/IPC Morphology 223
13.2.4	Surface Phenotype of pDCs/IPCs 224
13.3	pDC/IPC Development 224
13.4	Localization, Migration, and Lifespan of pDCs/IPCs 227
13.5	Innate Immune Response by pDCs/IPCs 228
13.5.1	pDCs/IPCs Selectively Express Intracellular TLR-7 and TLR-9 that Respectively Recognize Single-Stranded RNA and Double-Stranded DNA 228
13.5.2	pDCs/IPCs Are Professional Type 1 IFN-Producing Cells 229
13.5.3	pDCs/IPCs Rapidly Produce Large Amounts of IFN-α that Is Independent of Positive Feedback of IFN-β Through Type 1 IFN Receptors 230
13.5.4	TLR7/TLR9-mediated IFN-a production by pDCs/IPCs depends on Myd88-IRAK4-TRAF6-IRF-7 complexes 231
13.5.5	Human pDCs/IPCs Have a Limited Ability to Produce IL-12 231
13.5.6	Myeloid DCs Are Specialized in Producing IL-12, but not Type 1 IFNs 233
13.6	Regulation of T-cell-mediated Immune Responses by pDCs/IPCs 233
13.6.1	pDC/IPC Differentiation to Mature DCs through Two Pathways 233
13.6.2	pDC-Derived DCs Induce Th1 by IFN-α but not IL-12 235
13.6.3	pDC-Derived DCs Induce Th2 through OX40L 235
13.6.4	pDC-Derived DCs and their Ability to Prime Naïve versus Memory T Cells 235
13.6.5	pDC-Derived DCs and Presentation of Endogenous and Exogenous Antigens 235
13.6.6	pDCs/IPCs and Cross-priming 236

Contents	
13.6.7	pDCs/IPCs and Regulatory T Cells 236
13.7	pDCs/IPCs Regulate the Function of Conventional Myeloid DC by Type 1 IFN 237
13.8	Regulation of NK Cell Function by pDCs/IPCs 238
13.9	Regulation of B-cell Function by pDCs/IPCs 239
13.10	pDCs/IPCs and Human Diseases 239
13.10.1	HIV 239
13.10.2	Systemic Lupus Erythematosus (SLE) 239
13.10.3	Cancer 240
13.11	Conclusion 240
	Acknowledgments 241
	References 241
14	Monocyte subsets and their relation to DCs 253
	Brigitte Senechal, Darin Fogg, Gaelle Elain, and Frederic Geissmann
14.1	Monocytes and the Concept of the "Mononuclear Phagocyte System"
2	(MPS) 254
14.1.1	Blood Monocytes in the Mononuclear Phagocyte System 254
14.1.2	Plasticity of Monocytes as Studied in vitro and its Relevance to DC
	Differentiation in vivo 256
14.1.3	Contribution of Monocytes to Long-lived Resident Cells in Peripheral Tissues 257
14.1.4	Contribution of Monocytes to Short-lived Bone Marrow-derived Steady State Macrophages and DC 258
14.1.5	Evidence that Monocytes Contribute to Short-lived Migrating Dendrition
	Cells that Differentiate During Inflammation and Infection 259
14.1.6	Summary of the Respective Contribution of Monocytes to Individual
	Subsets of the MPS System 260
14.2	Molecular Determinants of Monocyte Differentiation 260
14.3.2	Monocyte Subsets 262
14.3.3	CCR2+ CX3CR1 ^{low} "Inflammatory" Monocytes 264
14.3.4	The Enigmatic CCR2 ⁻ CX3CR1 ^{high} Monocytes 265
14.3.5	Relationship Between CCR2+ CX3CR1low Monocytes and CCR2-
	CX3CR1 ^{high} Monocytes 266
14.3.6	Additional Subsets of Monocytes? 266
14.4	Migration of Monocytes and Their Recruitment to Tissues 267
14.4.1	Monocyte Entry into the Target Tissues 267
14.4.2	Baseline Extravasation of Monocytes 268
14.4.3	Recruiment of Monocytes During Inflammation and Infection 268
14.5	Concluding remarks 269
	Acknowledgments 270
	References 270

V	Dendritic Cell Migration 279
15	Steady State Migration of Dendritic Cells in Lymph 279
	Gordon MacPherson, Simon Milling, Emma Turnbull and Ulf Yrlid
15.1	Introduction 279
15.1.1	Dendritic Cells 279
15.1.2	Why Study Lymph Dendritic Cells? 280
15.1.3	Lymphatic Terminology 280
15.1.4	Historical 281
15.2	Dendritic Cells in the Periphery 281
15.2.1	Constitutive Migration of Dendritic Cells from Peripheral Tissues 281
15.2.2	Exit of Dendritic Cells from Peripheral Tissues 282
15.2.3	Entry of Dendritic Cells into Peripheral Lymph 282
15.3	Lymph Dendritic Cells 282
15.3.1	Pseudo-afferent Lymph 282
15.4	Properties of Lymph Dendritic Cells in the Rat 283
15.4.1	Steady-state Output 283
15.4.2	Origin of Afferent Lymph Dendritic Cells 283
15.4.3	Steady-state Rat Lymph Dendritic Cells are "Semi-mature" 284
15.4.4	Subsets of Rat Lymph Dendritic Cells 284
15.4.5	Migratory Fate of Lymph Dendritic Cells 285
15.4.6	Uptake and Transport of Apoptotic Cells by Intestinal Dendritic
	Cells 286
15.5	Dendritic Cells and B Cells 286
15.6	Dendritic Cells and the Pathogenesis of Transmissible Spongiform
	Encephalopathies (TSE) 287
15.7	Conclusions 288
	References 288
16	Multiple Pathways to Control DC Migration 295
-	Karel Otero, Elena Riboldi, Annalisa Del Prete, Annunciata Vecchi,
	Fabio Facchetti, Alberto Mantovani and Silvano Sozzani
16.1	Dendritic Cells as Professional Migratory Cells 295
16.2	Role of Chemokines in the Recruitment of Myeloid and Plasmacytoid
	Dendritic Cells 296
16.3	Migration of Mature Dendritic Cells to Secondary Lymphoid
	Organs 298
16.4	Chemotactic Factors for Dendritic Cells: more than Chemokines 301

Tuning Dendritic Cell Migration by Nonchemotactic Signals 303

Concluding Remarks 305

Acknowlegements 305 References 306

16.5

16.6

χVI	Cor

XVI Co	ents	
' vı	T-cell Activation and Co-stimulation 313	
17	Antigen Processing and Presentation: CD1d and NKT cells 313 Serani L.H. van Dommelen, Dale I. Godfrey and Mark J. Smyth	
17		
17		
	2.1 The CD1d Molecule 313	
	2.2 Nature of CD1d and Glycolipid Recognition by TCR 315	
17	2.3 Nature of CD1d-expressing APC 316	
17		
17	3.1 Defining NKT Cells 318	
17	3.2 Tissue Location and NKT Cell Subsets 319	
17	Nature of the Antigens Presented by CD1d-expressing APC to NKT Cells 319	
17	4.1 Self-ligands 320	
17	1.2 Naturally-occurring Exogenous Ligands 320	
17	4.3 Synthetic Ligands 321	
17	Effector Functions of NKT Cells 321	
17	5.1 Cytokine Secretion and Cytotoxicity of NKT Cells 322	
17	The Initial Cross-talk Between CD1d-expressing APC and NKT Cells 322	
	Functional Diversity of NKT Cell Responses 323	
17	Modulation of Downstream Immune Responses by a-GalCer-activate Cells 325	ed
17	5.5 Adjuvant-like Effect of NKT Cells on DC Mediated Antigen Presentation 327	
17	Role of CD1d-restricted NKT Cells in Disease Models 328	
17		
	Acknowledgments 328 References 329	
18	The Role of Dendritic Cells in T-cell Activation and Differentiation 34 Federica Sallusto and Antonio Lanzavecchia	13
18		
18	Requirements for Activation of Naïve T Lymphocytes 343	
18	2.1 Co-stimulatory and Inhibitory Pathways 345	
18	2.2 Differentiation to Effector T Cells 345	
18	Dendritic Cell Maturation 346	
18	T-cell Priming by Dendritic Cells 347	
18	1 Priming of Th1 and Inflammatory T-cell Responses 348	
18	Priming of Th2 Cells 348	
18	3 Imprinting Tissue Homing Receptors 349	
	The Role of Plasmacytoid Dendritic Cells in T-cell Responses 349	
18	Concluding Remarks 350	
	References 350	

19	Cytokines Produced by Dendritic Cells 355
	David F. Tough
19.1	Introduction 355
19.2	DC Cytokine Expression: A Few Caveats 355
19.3	Type I Interferon 356
19.4	IL-12, IL-23, IL-27 357
19.5	IL-18 359
19.6	IL-6 360
19.7	IL-1 360
19.8	TNF-α 362
19.9	Concluding Remarks 363
	Acknowledgement 364
	References 364
Volume 2	
VII	Th1 and Th2 Decision 385
20	The Plasticity of Dendritic Cells Populations in Promoting Th-cell
	Responses 385
	André Boonstra, Giorgio Trinchieri and Anne O'Garra
20.1	Effector Th-cell Populations 385
20.2	Factors Inducing the Development of Th1 or Th2 Cells 386
20.2.1	The Strength of DC–Th-cell Interaction 387
20.2.2	Co-stimulators 388
20.2.3	Genetic Background 388
20.3	Opposing Concepts: Pre-programmed versus Flexible DC Direct
	Th-cell Development 388
20.3.1	Mouse Dendritic Cell Populations in Directing Th-cell
	Development 388
20.3.2	Human Dendritic Cell Populations in Directing Th-cell
	Development 390
20.4	Differential TLR Expression by Distinct Dendritic Cell Populations 392
20.4.1	Modulation of TLR Expression 392
20.5	Modulation of IL-12p70 or IFN-α Production 393
20.6	Factors Responsible for Driving Th2-cell Development 395
20.7	Modulation by Tissue Factors 395
20.8	Concluding Remarks 396
	References 397
21	Microbial Instruction of Dendritic Cells 405
	Esther C. de Jong, Hermelijn H. Smits, Eddy A. Wierenga and
	Martien L. Kapsenberg
21.1	Introduction 405
21.2	Effector Th1 and Th2 Cells and Regulatory T Cells 405
~1.2	7

XVIII	Contents	
•	21.3	Dendritic Cells and Pattern Recognition Receptors 406
	21.4	DC-derived Factors that Promote Th1, Th2 or Regulatory T-cell
		Responses 408
	21.4.1	Th1 Cell-promoting Factors 408
	21.4.2	Th2 Cell-promoting Factors 410
	21.4.3	Regulatory T-cell-promoting Factors 410
	21.5	TLR-mediated Activation of DC by Microbes and their
		Compounds 411
	21.5.1	TLR2 411
	21.5.2	TLR3 412
	21.5.3	TLR4 412
	21.5.4	TLR5 413
	21.5.5	TLR7/8 413
	21.5.6	TLR9 413
	21.5.7	TLR10/11 414
	21.6	Th1 Cell-promoting DC 414
	21.7	Th2 Cell-promoting DC 415
	21.8	Regulatory T-cell-promoting DC 415
	21.9	Indirect Priming of DC 416
	21.10	Concluding Remarks 417
		References 417
	VIII	CTL Priming and Crosspresentation 427
	VIII 22	Crossprocessing and Crosspresentation 427
	22 22.1	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427
	22	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj
	22.1 22.2 22.2.1	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428
	22.1 22.2 22.2.1 22.2.2	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430
	22.1 22.2 22.2.1 22.2.2 22.2.2	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430 Apoptotic Cells 430
	22.1 22.2 22.2.1 22.2.2 22.2.2.1 22.2.2.1 22.2.2.2	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430 Apoptotic Cells 430 Necrotic Cells 432
	22.1 22.2 22.2.1 22.2.2 22.2.2.1 22.2.2.2 22.2.2.2 22.2.2.3	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430 Apoptotic Cells 430 Necrotic Cells 432 Heat-shock Proteins 432
	22.1 22.2 22.2.1 22.2.2 22.2.2.1 22.2.2.2 22.2.2.3 22.2.2.4	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430 Apoptotic Cells 430 Necrotic Cells 432 Heat-shock Proteins 432 Immune Complexes 433
	22.1 22.2 22.2.1 22.2.2 22.2.2.1 22.2.2.2 22.2.2.3 22.2.2.4 22.2.2.5	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430 Apoptotic Cells 430 Necrotic Cells 432 Heat-shock Proteins 432 Immune Complexes 433 Nibbling from Live Cells 434
	22.1 22.2 22.2.1 22.2.2 22.2.2.1 22.2.2.2 22.2.2.3 22.2.2.4 22.2.2.5 22.2.2.6	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430 Apoptotic Cells 430 Necrotic Cells 432 Heat-shock Proteins 432 Immune Complexes 433 Nibbling from Live Cells 434 Exosomes 434
	22.1 22.2 22.2.1 22.2.2 22.2.2.1 22.2.2.2 22.2.2.3 22.2.2.4 22.2.2.5 22.2.2.6 22.2.2.7	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430 Apoptotic Cells 430 Necrotic Cells 432 Heat-shock Proteins 432 Immune Complexes 433 Nibbling from Live Cells 434 Exosomes 434 TLR and MyD88 involvement in Crosspresentation 435
	22.1 22.2 22.2.1 22.2.2 22.2.2.1 22.2.2.2 22.2.2.3 22.2.2.4 22.2.2.5 22.2.2.6 22.2.2.7 22.3	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430 Apoptotic Cells 430 Necrotic Cells 432 Heat-shock Proteins 432 Immune Complexes 433 Nibbling from Live Cells 434 Exosomes 434 TLR and MyD88 involvement in Crosspresentation 435 Mechanisms of Crossprocessing and Crosspresentation 436
	22.1 22.2 22.2.1 22.2.2 22.2.2.1 22.2.2.2 22.2.2.3 22.2.2.4 22.2.2.5 22.2.2.6 22.2.2.7 22.3 22.3.1	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430 Apoptotic Cells 430 Necrotic Cells 432 Heat-shock Proteins 432 Immune Complexes 433 Nibbling from Live Cells 434 Exosomes 434 TLR and MyD88 involvement in Crosspresentation 435 Mechanisms of Crossprocessing and Crosspresentation 436 Entry into the Classical Endocytic Pathway 436
	22.1 22.2 22.2.1 22.2.2 22.2.2.1 22.2.2.2 22.2.2.3 22.2.2.4 22.2.2.5 22.2.2.6 22.2.7 22.3 22.3.1 22.3.2	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430 Apoptotic Cells 430 Necrotic Cells 432 Heat-shock Proteins 432 Immune Complexes 433 Nibbling from Live Cells 434 Exosomes 434 TLR and MyD88 involvement in Crosspresentation 435 Mechanisms of Crossprocessing and Crosspresentation 436 Entry into the Classical Endocytic Pathway 436 Phagosome—endosome Compartment 438
	22.1 22.2 22.2.1 22.2.2 22.2.2.1 22.2.2.2 22.2.2.3 22.2.2.4 22.2.2.5 22.2.2.6 22.2.2.7 22.3 22.3.1 22.3.2 22.3.3	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430 Apoptotic Cells 430 Necrotic Cells 432 Heat-shock Proteins 432 Immune Complexes 433 Nibbling from Live Cells 434 Exosomes 434 TLR and MyD88 involvement in Crosspresentation 435 Mechanisms of Crossprocessing and Crosspresentation 436 Entry into the Classical Endocytic Pathway 436 Phagosome—endosome Compartment 438 A Special Mechanism for Soluble Antigens? 439
	22.1 22.2 22.2.1 22.2.2 22.2.2.1 22.2.2.2 22.2.2.3 22.2.2.4 22.2.2.5 22.2.2.6 22.2.7 22.3 22.3.1 22.3.2	Crossprocessing and Crosspresentation 427 Mojca Škoberne and Nina Bhardwaj Introduction 427 Acquisition of Antigens for Crosspresentation 428 Cells that Crosspresent 428 Sources of Antigens and Receptors involved in Crosspresentation 430 Apoptotic Cells 430 Necrotic Cells 432 Heat-shock Proteins 432 Immune Complexes 433 Nibbling from Live Cells 434 Exosomes 434 TLR and MyD88 involvement in Crosspresentation 435 Mechanisms of Crossprocessing and Crosspresentation 436 Entry into the Classical Endocytic Pathway 436 Phagosome—endosome Compartment 438

22.4	Physiological Relevance of Crosspresentation 442
	Acknowledgements 442
	References 443
23	A Systems Biologist's View of Dendritic Cell-Cytotoxic T Lymphocyte
	Interaction 455
	Burkhard Ludewig and Gennady Bocharov
23.1	Introduction 455
23.2	Deciphering the Systems Biologist's Approach 456
23.2.1	Modularity and Protocols 457
23.2.2	Feedback Control 458
23.2.3	Redundancy 460
23.2.4	Structural Stability 461
23.3	From Systems Biology to DC–CTL Immunobiology 461
23.3.1	Dynamics of CTL Activation and Differentiation 462
23.3.2	Multiple Levels of Positive and Negative Feedback Control 463
23.3.2.1	Managing DC Recruitment and Antigen Translocation 464
23.3.2.2	Elimination of DCs by Effector CTL 464
23.3.2.3	Rapid Amplification of Signals through Molecular "Ping-Pong"
	Interactions 464
23.3.2.4	Limiting the CTL "Overshoot" through Feedforward Control 465
23.3.3	DC Subsets Provide Redundant Activating Signals 466
23.3.4	Tuning of Dendritic Cell Activation 468
23.3.4.1	Excitement through Pattern Recognition 468
23.3.4.2	DC Tuning and Tolerance to Self-antigens 469
23.4	Conclusions 470
	Acknowledgments 470
	References 471
IX	Dendritic Cells Cross-talk with Other Cell Types 481
24	Dendritic Cells and Natural Killer Cells 481
24	Magali Terme and Laurence Zitvogel
24.1	Introduction on NK Cells 481
24.1	Activation of NK Cells by DC 482
24.2.1	NK-cell Activation and DC Subsets 483
24.2.1	Molecular Mechanisms of the DC-mediated NK-cell Activation 483
24.2.2	Reciprocal Interaction of DC and NK Cells 484
24.3.1	DC Maturation Induced by NK Cells 485
24.3.1	Lysis of DC by Activated NK Cells 485
24.3.2 24.4	Where do DC Meet NK Cells? 486
24.4.1	In Lymph Nodes 486
24.4.1	· -
	In the Periphery 487 DC/NK Cross-talk and T Lymphocytes 487
24.5	DC/11K C1055-talk and 1 Lymphocytes 70/

xx	Contents	
•	24.5.1	Bridging Innate and Adaptive Immunity 487
	24.5.2	Modulation of the DC/NK-cell Cross-talk by CD4 ⁺ CD25 ⁺ Regulatory T Cells and Conventional T Cells 489
	24.6	The DC/NK-cell Cross-talk in Physiopathology 490
	24.6.1	In Infectious Diseases 490
	24.6.1.1	Viral Infections 490
	24.6.1.2	Bacterial Infections 491
	24.6.2	In Cancer 491
	24.7	Concluding Remarks 493
		References 494
	25	Intercellular Communication via Protein Transfer 499
	05.4	Marca H.M. Wauben
	25.1	What are Exosomes, and Where do they Come From? 499
	25.2	Which Cells are Targets for Exosomes, and how do Exosomes Interact with these Cells? 500
	25.3	What is the Consequence of Exosome Binding or Uptake for the Target Cell? 501
	25.4	What is the Physiological Role of Exosomes in the Immune System? 502
	25.5	Cell-Cell Contact-dependent Transfer of Membrane Proteins 504
	25.6	How are Membrane Proteins Transferred Between Immune Cells, and What is their Fate? 506
	25.7	What is the Physiological Role of Membrane Protein Swapping in the
	25.8	Immune System? 508
	23.0	Concluding Remarks 509 Abbreviations 509
		References 510
		Activities 510
	X	Tolerogenic Dendritic Cells 517
	26	Differentiation Stages and Subsets of Tolerogenic Dendritic Cells 517
		Manfred B. Lutz
	26.1	Introductory Remarks 517
	26.2	Mechanisms of T-cell Tolerance Induction 518
	26.2.1	Ignorance 519
	26.2.2	Anergy 519
	26.2.3	Deletion 519
	26.2.4	Immune Deviation 520
	26.2.5	The Concept of "Immune Balance" 520
	26.2.6	Regulation/suppression 521

26.2.7

26.3

26.3.1

Combinations 521

Thymic DC 522

Tolerogenic DC Subsets in vivo 522

26.3.2	DC in Lymph Nodes and Spleen 523
26.3.3	Migratory DC from Peripheral Organs 523
26.3.4	Plasmacytoid DC 524
26.4	DC Precursors 524
26.5	Immature DC 525
26.5.1	Tissue Resident DC 525
26.5.2	Induction of T-cell Anergy by Immature DC 525
26.5.3	Maturation Inhibitors 526
26.5.4	Maturation Resistance 526
26.6	Semi-mature DC 528
26.6.1	Steady-state Migratory DC 530
26.7	Fully Mature DC 531
	Acknowledgements 531
	Abbreviations 531
	References 532
	- 100 m Haar 1 100 - 50 mt le tel and Manager la deal Accepta
27	Dendritic Cell Manipulation with Biological and Pharmacological Agents
	to Induce Regulatory T Cells 545
27.4	Luciano Adorini and Giuseppe Penna
27.1	Introduction 545 Mechanisms Promoting Tolerogenic Dendritic Cells 546
27.2	Wiceimmin 1 Tomoung 1 orer of control 2 or c
27.2.1	Indoleamine 2,3-dioxygenase 547
27.2.2	Immunoglobulin-like Transcripts 547
27.3	Induction of Tolerogenic Dendritic Cells 548
27.3.1	Biological Agents Promoting Tolerogenic Dendritic Cells 549
27.3.1.1	IL-10 549
27.3.1.2	ТGF-β 550
27.3.1.3	TNF-α 550
27.3.1.4	G-CSF 551
27.3.2	Pharmacological Agents Promoting Tolerogenic Dendritic Cells 551
27.4	Induction of Tolerogenic Dendritic Cells by VDR Agonists 553
27.4.1	Tolerogenic Dendritic Cells Induced by VDR Agonists lead to
	enhancement of regulatory T cells 555
27.4.2	Upregulation of Inibitory Receptor Expression in Dendritic Cells by
	VDR agonists 556
27.4.3	Modulation of Chemokine Production by VDR Agonists can affect
	Recruitment of Effector T cells and CD4+CD25+ Ts cells to
	Inflammatory Sites 557
27.5	Common Features of Agents Leading to Induction of Tolerogenic
	DCs 558
27.6	Conclusions 559
	References 560

28	Surface Molecules Involved in the Induction of Tolerance by Dendritic Cells 569
	Laura C. Bonifaz
28.1	Introduction 569
28.2	Dendritic Cells and Central Tolerance 570
28.3	Dendritic Cells and Peripheral Tolerance 570
28.4	C-type Lectin Receptors 571
28.4.1	Advantages of DEC-205 as an Endocytic Receptor for Antigen
	Presentation 572
28.4.2	DEC-205: an Endocytic Receptor that Preserves the Steady State in the
	DC after the Capture of the Antigen 573
28.5	Induction of Peripheral Tolerance by Resting Dendritic Cells 573
28.5.1	The Same Dendritic Cells Could Operate in the Induction of
	Immunity 574
28.5.2	The Induction of Tolerance by Steady-state Dendritic Cells Promotes
	Avoidance of the Induction of Autoimmunity 574
28.5.3	Surface Molecules are Involved in Peripheral Tolerance Induction by
	Resting Dendritic Cells through DEC-205 575
28.5.4	Additional Evidence Supports the Role of Resting DC in the Induction
	of Peripheral Tolerance 575
28.6	Surface Molecules Involved in the Induction of Peripheral
	Tolerance 576
28.7	Other Receptors Involved in the Induction of Tolerance that can
	Preserve the Resting of DC or Induce Negative Signaling 577
28.7.1	Integrins 577
28.7.2	Fc Receptors 578
28.7.3	Suppressor and Regulatory T Cells 578
28.8	Notch Ligands as Surface Molecules Involved in the Induction of
	Regulatory T Cells 579
28.9	ILT-3 and ILT-4: Two Inhibitory Molecules Involved in Tolerance
	Induction 580
28.10	Special DC for Tolerance? 581
28.11	Regulatory–tolerogenic DC 582
28.12	Concluding Remarks 582
	Acknowledgments 583
	References 583
20	
29	Interaction Between Dendritic Cells and Apoptotic Cells 591
20.1	Adriana T. Larregina and Adrian E. Morelli
29.1	Introduction 591
29.2	Dendritic Cells Phagocytose and Process Apoptotic Cells 592
29.3	The Phagocytic Synapse 593
29.3.1 29.3.2	Externalized Phosphatidylserine (PS) and Receptors for PS 595
47.J.L	Thrombospondin-1 (TSP-1), CD36 and the Integrins $\alpha_{\nu}\beta_{3}$
	and $\alpha_{\nu}\beta_{5}$ 596

20.2.2	Complement Footons and Complement December (CD) 500
29.3.3	Complement Factors and Complement Receptors (CR) 596
29.3.4	Pentraxins 598 Mills for Clabric Protein Englanmed Crowth Factor 8
29.3.5	Milk-fat Globule Protein Epidermal Growth Factor 8 (MFG-E8)/lactadherin 598
29.3.6	Other Apoptotic Cell Recognition Signals 599
29.4	Redundant Receptors and Backup Mechanisms for Apoptotic Cell Clearance 600
29.5	Regulatory Effects of Early Apoptotic Cells on Dendritic Cells 600
29.6	Molecular Mechanisms of the Interaction between Dendritic Cells and Apoptotic Cells 602
29.7	Dendritic Cells, Apoptotic Cells and Peripheral Tolerance 603
29.8	The Potential Therapeutical Use of Apoptotic Cells for Peripheral Tolerance 605
29.9	Pathogens and Apoptotic Cell-like Mimicry 607
29.10	Dead Cells and the Delicate Balance between Immunity and
	Tolerance 608
29.11	Concluding Remarks 610
	Acknowledgements 610
	References 611
30	Pharmacologically Modified Dendritic Cells: A Route to
30	Tolerance-associated Genes 619
	Kathleen F. Nolan, Stephen F. Yates, Alison M. Paterson, Paul J. Fairchild
	and Herman Waldmann
30.1	Dendritic Cells, Maturation and Tolerance 619
30.2	Gene Profiling 622
30.2.1	Gene Profiling Technologies 623
30.2.2	Serial Analysis of Gene Expression (SAGE) 624
30.2.2.1	SAGE Methodology 625
30.2.2.2	Handling Raw SAGE Data 627
30.2.3	Accumulation of a Comparative SAGE Resource for Identifying
30.2.3	Tolerance-associated Genes 628
30.2.3.1	Relationship of Modulated DC Populations based on Gene Expression
	Patterns 631
30.2.3.2	Elucidation of "Signatures" of Genes Associated with Tolerance 632
30.2.3.3	Identification of Novel Genes 634
30.2.3.4	AQ4 SAGE Library Comparisons Provide Insights to Biological
	Mechanism 634
30.3	Downstream Assessment of Tolerance Associated Candidate
30.3	Genes 636
30.3.1	Simultaneous Assessment of Multiple Candidate Gene Expression
	Levels using a Custom "Immunochip" 636
30.3.2	Assessing the Functional Relevance of Tolerance Candidates by
	Genetic Manipulation of DCs 637

xxıv	Contents	
	30.3.3	Assessing the Functional Impact of Candidates in an <i>in vivo</i> Tolerance Model 638
	30.4	Downstream Clinical Relevance 638 References 639
	Part B	Dendritic Cells in Disease 649
	ΧI	Parasites 651
	31	Malaria 651
		Britta C. Urban and Francis M. Ndungu
	31.1	Introduction to Malaria 651
	31.2	Antigenic Variation 652
	31.3	Animal Models for Malaria 653
	31.4	Acquired Immunity to Malaria 653
	31.4.1	Immune Response to Liver Stages 654
	31.4.2	Cellular Immunity to the Erythrocytic Stage 654
	31.4.3	Humoral Immunity to the Erythrocytic Stage 655
	31.5	Immune Recognition of iRBC 656
	31.5.1	Toll-like Receptors 656
	31.5.2	CD36 657
	31.5.3	Other Scavenger Receptors 658
	31.5.4	Complement and Fc Receptors 658
	31.6	Dendritic Cells in Malaria 658
	31.6.1	DCs in Human Malaria 658
	31.6.2	DCs in Rodent Malaria 659
	31.7	Synopsis 660
		Acknowledgments 662
		References 663
	32	Dendritic Cells in Leishmaniasis: Regulators of Immunity and Tools for
		New Immune Intervention Strategies 669
		Heidrun Moll
	32.1	Introduction 669
	32.2	Mechanisms Mediating Resistance or Susceptibility to
		Leishmaniasis 670
	32.2.1	The Role of T Helper Cell Subsets 671
	32.2.2	The Role of Regulatory T Cells 672
	32.3	Dendritic Cell Interaction with Leishmania Parasites 673
	32.3.1	Parasite Uptake by Dendritic Cells 673

Subcellular Location of Leishmania Parasites in Dendritic Cells 674

Dendritic Cell Subsets Involved in the Uptake of Leishmania 675

Dendritic Cell Migration and Induction of a Leishmania-specific

Dendritic Cells in Leishmania-infected Tissues 676

Immune Response 676

32.3.2

32.3.3

32.3.4

32.4

32.4.1	The Role of Chemokines and Chemokine Receptors Expressed by Dendritic Cells 677
32.4.2	Transport and Presentation of <i>L. major</i> Antigen by Dendritic
	Cells 678
32.4.3	Parasite Persistence in Immune Hosts 680
32.5	Regulation of the Leishmania-specific Immune Response by Dendritic
	Cells 680
32.5.1	The Role of IL-12 Production by Dendritic Cells 681
32.5.2	Other Parameters that may Govern the Polarization of
	T Helper Cells 682
32.6	Parasite Evasion of Dendritic Cell Function 683
32.7	Dendritic Cells as Tools for Novel Immune Intervention Strategies
	Against Leishmaniasis 685
32.7.1	Dendritic Cell-based Vaccination and Immunotherapy 685
32.7.2	Parameters Determining the Efficacy of Dendritic Cell-based Immune
	Intervention Strategies 686
32.8	Conclusions and Perspectives 687
	References 688
33	Sentinel and Regulatory Functions of Dendritic Cells in the Immune
33	Response to Toxoplasma gondii 693
	Alan Sher, Felix Yarovinsky, Romina Goldszmid, Julio Aliberti and
	Dragana Jankovic
33.1	Introduction 693
33.2	Activation of DC by T. gondii 694
33.2.1	Responsive DC Subpopulations 694
33.2.2	Host Receptors and Parasite Ligands Involved in Triggering of Murine
	DC 696
33.2.3	Activation of Human DC 698
33.3	Regulation of DC Activity 699
33.4	Role of DC in T. gondii-induced Immune Polarization 700
33.5	Mechanisms of Antigen Presentation to T Cells 702
33.6	Towards an Understanding of DC Function in vivo 703
	Acknowledgements 704
	References 705
34	Schistosoma 709
	Andrew S. MacDonald and Edward J. Pearce
34.1	Introduction 709
34.2	DC Response to Schistosome Ag 710
34.3	Th2 Induction by DC in Response to Schistosome Ag 714
34.4	DC During Schistosome Infection 717
34.5	Discussion 718
	Acknowledgements 719
	References 719

αvi	Contents

XII	Bacteria 723		
35	Dendritic Cells and Immunity to Salmonella 723		
35.1	Mary Jo Wick Introduction 723		
35.1 35.2			
35.2 35.3	Dendritic Cell Subsets, Short and Sweet 724 Dendritic Cells and Salmonella: Lessons from <i>in vitro</i> Studies 724		
35.3.1	Bacterial Uptake and the Fate of Internalized Bacteria 724		
35.3.1			
35.3.2.1	Presentation of Salmonella Antigens by Dendritic Cells 727 Processing of Salmonella for Direct Presentation on MHC-II by Infected Dendritic Cells 727		
35.3.2.2	Processing of Salmonella for Direct Presentation on MHC-I by Infected Dendritic Cells 727		
35.3.2.3	Modulating of Antigen Presentation by Salmonella 728		
35.3.2.4	Waste not, Want not: Dendritic Cells as Bystander Antigen-presenting Cells 729		
35.4	Time to go to Work: Salmonella-induced Dendritic Cell Maturation 730		
35.5	Murine Infection Models to Study Dendritic Cell Interaction with		
	Salmonella in vivo 733		
35.5.1	Salmonella Infection and Penetration of the Intestinal		
25.5.2	Epithelium 733		
35.5.2 35.5.3	Dendritic Cell Take-up Salmonella <i>in vivo</i> 734 Getting the Game Started: Dendritic Cells Initiate Adaptive Immunity		
25 5 2 4	to Salmonella 734		
35.5.3.1	Salmonella-induced Dendritic Cell Maturation During Infection 734		
35.5.3.2	Presentation of Salmonella Antigens by Dendritic Cells in vivo 736		
35.6	Concluding Remarks 737		
	Acknowledgements 737		
	References 738		
36	Dendritic Cells in Tuberculosis 745		
	Ulrich E. Schaible and Florian Winau		
36.1	Introduction 745		
36.2	Tuberculosis 745		
36.3	Mycobacteria are Intracellular Pathogens 747		
36.4	Dendritic Cells Present Antigens in Tuberculosis 749		
36.5	Dendritic Cells are Regulatory Cells in Tuberculosis 752		
36.6	Dendritic Cells and Cross-Priming 753		
36.7	Mycobacteria Interfere with Antigen Presenting Cell Function 755		
36.8	Conclusion 756		
	Acknowledgement 756		
	References 756		

3/	Dendritic Cell-Epithelial Cell Interactions in Response to Intestinal
	Bacteria 759
	Maria Rescigno
37.1	The Intestinal Epithelium and the Gut-associated Lymphoid Tissue (GALT) 759
37.2	Antigen Uptake in the Gut and DC Populations 760
37.3	Cross-talk between Bacteria and Epithelial Cells 762
37.4	Unique Functions of Mucosal DCs 763
37.5	Intestinal Immune Homeostasis is Regulated by the Cross-talk
	between ECs and DCs 764
37.6	Cross-talk between ECs and DCs in Bacterial Handling 766
37.7	Conclusions 767
	References 767
Volume 3	3
XIII	Viruses 773
38	Sleeping with the Enemy: The Insidious Relationship between Dendrition
	Cells and Immunodeficiency Viruses 773
	L. Vachot, S.G. Turville, S. Trapp, S. Peretti, G. Morrow, I. Frank and
	M. Pope
38.1	Introduction 773
38.1.1	The Global AIDS Epidemic 773
38.1.2	Overview of Dendritic Cell Involvement in the Onset and Spread of HIV Infection 774
38.1.3	In vivo Evidence for DC Involvement in HIV Infection 776
38.1.3.1	Macaque Studies on Mucosal DCs and Infection 776
38.1.3.2 38.2	Changes in DC Biology in Immunodeficiency Virus Infection 777 Consequences of DC–HIV Interplay 778
38.2.1	HIV-binding Receptors Expressed by DCs 778
38.2.2	HIV Infection of DCs 780
38.2.3	Internalization of HIV Particles by DCs 782
38.3	DC-to-T-cell Transmission of Infectious Virus 783
38.3.1	Immunodeficiency Virus Replication in the DC-T Cell Milieu 783
38.3.2	Virus Movement across DC-T-cell Synapses 784
38.3.3	Two Phases of Virus Spread from DCs to T Cells 786
38.4	Inhibiting DC-driven Infection 788
38.4.1	Preventing direct HIV Interactions with DCs and DC-T-Cell
	Mixtures 788
38.4.2	DC-mediated HIV Transmission to T cells 789
38.5	Functional Modification of DCs by HIV Favors Infection over Immunity 790
38.5.1	Viral Factors Modify moDCs 790
	•

38.5.1

XXVIII	Contents	
•	38.5.2 38.5.3	Effects of Virus on Circulating DC Subsets 791 Virus-carrying Immature DCs Activate Substandard Virus-specific T-cell Responses 792
	38.6	Implications for Vaccine and Microbicide Strategies 793
	38.6.1	Blocking Mucosal Infection 793
	38.6.2	Using DCs to Boost Immunity 794
	38.6.2.1	DC-induced Primary Responses for Preventative HIV Vaccines 795
	38.6.2.2	DC-based Therapeutic Control of Existing Immunodeficiency Virus Infection 796
	38.7	Summary and Future Perspectives 797
		Acknowledgements 797
		References 797
	39	Cytomegalovirus Infection of Dendritic Cells 813 Brigitte Sénéchal and James W. Young
	39.1	Introduction 813
	39.2	HCMV Induces Immunosuppression 813
	39.3	A Role for Dendritic Cells in the Pathology of CMV Infection 814
	39.4	The Myeloid Lineage and Monocytes are Major Sites of HCMV Latency 814
	39.5	Human Dendritic Cells are a Potential Target for HCMV 815
	39.6	In vitro Evidence for HCMV Entry and Replication into Dendritic Cells 816
	39.7	HCMV Impairs the Function of Immature Dendritic Cells 817
	39.8	HCMV Impairs the Function of Mature Dendritic Cells 818
	39.9	Langerhans-type Dendritic Cells are also Permissive to HCMV 819
	39.10	Importance of Viral IL-10 in HCMV-induced Immunosuppression 820
	39.11	CMV Infection of Dendritic Cells in the Mouse Model 820
	39.12	Conclusion 822
		Acknowledgements 823
References 823		References 823
	40	Interactions of Hemorrhagic Fever Viruses with Dendritic Cells 829 Stefan Pöhlmann
	40.1	Introduction 829
	40.2	Filoviruses 830
	40.2.1	Pathology and Epidemiology 830
	40.2.2	Replication 831
	40.2.3	Tropism 832
	40.2.4	Dendritic Cells are Major Targets of Ebolavirus 832
	40.2.5	Filovirus Infection causes Aberrant Dendritic Cell Maturation 833
	40.2.6	Filoviral Protein(s) Suppress Dendritic Cell Maturation 834
	40.3	Dengue Virus (DEN) 835
	40.3.1	Epidemiology and Pathology 835

40.3.2	Replication 836
40.3.3	Dengue Hemorrhagic Fever 836
40.3.4	Skin Dendritic Cells are Early Targets of Dengue Virus 837
40.3.5	Differential Effects of Dengue Virus on Infected and Bystander
	Dendritic Cells 837
40.4	Lassa Virus (LV) 839
40.5	Hantavirus (HTV) 840
40.6	Filoviruses and DEN Engage DC-SIGN, a Lectin Expressed on DCs 841
40.6.1	DC-SIGN – a Portal for Pathogens 841
40.6.2	Does DC-SIGN Promote Filovirus Infection in vivo? 842
40.6.3	DC-SIGNR – a DC-SIGN-related Attachment Factor that might
	Concentrate Filoviruses in Liver and Lymph Nodes 844
40.6.4	Dengue Virus Targets Dendritic Cells via DC-SIGN 844
40.7	Conclusions 845
	Acknowledgements 846
	Abbreviations 846
	References 847
41	Dendritic Cells in Measles Virus Pathogenesis 855
	Marion Abt, Nora Mueller and Sibylle Schneider-Schaulies
41.1	General Introduction 855
41.2	The Virus: Structure and Genotypes 856
41.3	The Role of Entry Receptors in Measles Virus Pathogenesis 857
41.4	Dendritic Cells in Measles Virus Pathogenesis 859
41.4.1	Measles Virus Interaction with Receptors on Dendritic Cells and
	Functional Consequences 860
41.4.1.1	Interaction with Surface Receptors 860
41.4.1.2	Functional Consequences of Measles Virus Surface Interaction with
	Dendritic Cells 861
41.4.2	Impact of Measles Virus on Dendritic Cell Viability and
	Maturation 862
41.4.3	Impact of Measles Virus on External Maturation/Stimulation Signals
	in Dendritic Cells 863
41.4.4	Impact of Dendritic Cells Measles Virus Infection on T-cell Viability,
	Activation and Expansion 864
41.5	Conclusions and Perspectives 865
	Acknowledgment 867
	Abbreviations 868
	References 868
42	Dendritic Cells and Herpes Simplex Virus Type 1 875
	Alexander T. Prechtel and Alexander Steinkasserer
42.1	The Herpes Simplex Virus Type 1 875
42.1.1	A Well-known Plaque for Centuries 875

xxx	Contents	
•	42.1.2	The Role of Viral Immediate-early Proteins During the Conquest of the Cell 875
	42.1.3	The Course of Herpes Simplex Virus Type 1 Infection and Replication 878
	42.2	Herpes Simplex Virus meets Dendritic Cells 879
	42.2.1	The Way into Dendritic Cells 879
	42.2.1.1	Receptors and Ligands for Cell Entry 879
	42.2.1.2	Infection of Different Dendritic Cell Populations by Herpes Simplex Virus Type 1 880
	42.2.2	Interference with Typical Functions of Dendritic Cells 881
	42.2.2.1	Interference with Dendritic Cell Maturation 881
	42.2.2.2	Interference with Dendritic Cell Migration 882
	42.2.2.3	Interference with Dendritic-cell-mediated T-cell Stimulation 884
	42.3	The Cell Surface Molecule CD83 885
	42.3.1	Characteristics of CD83 885
	42.3.2	Modulation of Dendritic Cell Function by Interference with CD83 mRNA Processing 886
	42.3.3	The Soluble Extracellular Domain of CD83 and its Influence on T-cell Proliferation 887
	42.3.4	The Function of Membrane-bound CD83 887
	42.3.5	Influence of CD83 on the T-cell Development in the Thymus 888
		Acknowledgements 889
		Abbreviations 889
		References 889
	43	Epstein-Barr Virus 897
		Christian Münz
	43.1	The Epstein-Barr Virus (EBV) 897
	43.2	Immune Control of Epstein–Barr Virus 898
	43.3	Stimulation of Lymphocyte Compartments Relevant to Epstein–Barr Virus Immune Control <i>in vitro</i> 899
	43.3.1	Tonsillar Natural Killer Cell Activation by Dendritic Cells and its Possible Role in Epstein–Barr Virus Infection 899
	43.3.2	Initiation of Epstein–Barr Virus-specific T-cell Immunity by Dendritic Cells 900
	43.4	Evidence for Priming of Epstein–Barr Virus Immune Control by Dendritic Cells in vivo 901
	43.4.1	Strong Th1 Polarization of CD4 ⁺ T-cell Responses to the Nuclear
	43.4.2	Antigen 1 of Epstein–Barr Virus (EBNA1) 901 Priming of Epstein–Barr Virus-specific Responses by Crosspresentation via Dendritic Cells Leads to Heterogeneous Affinity

Detection of Epstein-Barr Virus Infection by the Immune

of T-cell Responses 903

System 903

43.5

43.6	Immunotherapeutic use of Dendritic Cells against Epstein–Barr Virus 904	
43.7	Summary 905 References 906	
XIV	Fungi 915	
44	Dendritic Cells in Immunity and Vaccination against Fungi 915	
••	Luigina Romani and Paolo Puccetti	
44.1	Introduction 915	
44.2	Immunity to Fungi 916	
44.3	Dendritic Cells at the Host/Fungi Interface 917	
44.3.1	Fungal Recognition by Dendritic Cells and Receptor	
	Cooperativity 918	
44.3.2	Dendritic Cell Activation 921	
44.3.3	Dendritic Cell Conditioning 923	
44.3.3.1	Opsonins 923	
44.3.3.2	Tryptophan Metabolic Pathway 924	
44.3.3.3	T-cell Ligands 925	
44.3.3.4	Other Cells 925	
44.4	Dendritic Cells Translate Fungus-associated Information to Th1, Th2 and Treg Cells 926	
44.5	Exploiting Dendritic Cells as Fungal Vaccines 927	
44.6	Conclusions and Perspectives 928	
77.0	Acknowledgements 929	
	Abbreviations 929	
	References 930	
χv	Autoimmunity 935	
45	Dendritic Cells in Autoimmune Diseases 935	
	Alexis Mathian, Sophie Koutouzov, Virginia Pascual, A. Karolina Palucka	
	and Jacques Banchereau	
45.1	Introduction 935	
45.2	Dendritic Cells 936	
45.3	Dendritic Cells and Tolerance 936	
45.3.1	Central Tolerance 936	
45.3.2	Dendritic Cells and the Control of Peripheral Tolerance 938	
45.4	Dendritic Cell Activation and the Priming of Autoimmune Diseases 939	
45.4.1	Autoimmunity through Bystander Activation of Dendritic Cells 940	
45.4.1.1	Systemic Lupus Erythematosus as an IFN-a Driven Disease 941	
45.4.2	Defective Downregulation of Activated Dendritic Cells 942	
45.4.3	The Rise of "Autoimmune-prone" Dendritic Cell Subsets 942	

XXXII	Contents	
	45.5	Dendritic Cells Migrate into Inflammatory Sites and Maintain a Vicious Circle 945
	45.6	Dendritic Cells: Failure to Maintain Peripheral Tolerance 946
	45.7	A Special Role for Plasmacytoid Dendritic Cells in Systemic Lupus Erythemathosus 947
	45.7.1	Plasmacytoid Dendritic Cells as the Main Producer of Type I IFN in Systemic Lupus Erythemathosus 948
	45.7.2	Plasmacytoid Dendritic Cells Induce Plasma Cell Differentiation 948
	45.8	Dendritic Cells Fail to Delete Developing Autoreactive T Cells 949
	45.9	Autoimmunity Through Cytokine-induced Dendritic Cell Activation 949
	45.10	Different Cytokines Generate Different Dendritic Cells that may lead to Different Autoimmune Syndromes 950
	45.11	Concluding Remarks 951
		Acknowledgements 951
		References 952
	XVI	Transplantation 967
	46	Role of Dendritic Cells in Graft Rejection and Graft-versus-host Disease 967
		Véronique Flamand and Michel Goldman
	46.1	Alloantigen Presentation in Organ Transplantation 967
	46.1.1	Pathways of Alloantigen Recognition 967
	46.1.1.1	The Direct and Indirect Pathways 967
	46.1.1.2	The Semi-direct Pathway 969
	46.1.2	Sites of Alloantigen Presentation 970
	46.1.3	Factors Inducing Dendritic Cell Maturation and Migration 971
	46.1.3.1	Ischemia/reperfusion Injury 971
	46.1.3.2	Links between Innate and Adaptive Immunity during Allograft Rejection 972
	46.2	Alloantigen Presentation during Graft-versus-host Disease 973
	46.2.1	Dual Impact of Alloreactive T Cells during Graft-versus-host Disease 973
	46.2.2	Role of Host Dendritic Cells 974
	46.2.2.1	Host Dendritic Cells in the Initiation and Effector Phases of Graft-versus-host Disease 974
	46.2.2.2	Attempts to Eliminate Host Dendritic Cells 975
	46.2.2.3	The Effects of Recipient Conditioning on Dendritic Cell Maturation 975
	46.2.2.4	Reconstitution of Dendritic Cell ContentLAQ1L 976
	46.2.3	Role of Donor Dendritic Cells 977
		Acknowledgements 977
		References 978

47	Dendritic Cells and Transplantation Tolerance 983
	Paul J. Fairchild, Stephen F. Yates and Herman Waldmann 983
47.1	The Expanding World of Transplantation 983
47.2	The Role of Dendritic Cells in Allograft Rejection 985
47.2.1	Direct Presentation of Alloantigen 985
47.2.2	Indirect Presentation of Alloantigen 986
47.2.3	The Semi-direct Pathway of Alloantigen Presentation 987
47.2.4	Pathways of Antigen Presentation during Cell Replacement
	Therapy 988
47.3	The Role of Dendritic Cells in Self-tolerance 989
47.3.1	A Cell Type with Two Persona 989
47.3.2	Dendritic Cell Subsets Devoted to Tolerance 990
47.3.2.1	Dendritic Cells Expressing CD8α 990
47.3.2.2	Plasmacytoid Dendritic Cells 991
47.3.2.3	"Regulatory" Dendritic Cells 993
47.3.3	The Maturation Status of Dendritic Cells 994
47.3.3.1	Immature Dendritic Cells have an Enhanced Capacity to be
17131311	Tolerogenic 994
47.3.3.2	Maturation of Dendritic Cells as a Trigger Point for Immunity 996
47.4	Exploitation of Dendritic Cells for Transplantation Tolerance 997
47.4.1	Central Deletion of Alloreactive T Cells 997
47.4.2	Peripheral Regulation of Alloreactive T Cells 1000
47.4.3	Reinforcing a Tolerogenic Phenotype by Genetic Modification 1001
47.5	Prospects for the Induction of Tolerance via the Indirect
47.5	Pathway 1002
47.6	Immune Intervention in Cell Replacement Therapy 1005
47.6.1	Generation of Hematopoietic Stem Cells (HSC) for Mixed
	Chimerism 1005
47.6.2	Generation of Dendritic Cells for Tolerance Induction 1006
	References 1008
48	Dendritic Cells, Immune Regulation and Transplant Tolerance 1017
	Giorgio Raimondi and Angus W. Thomson
48.1	Introduction 1017
48.2	Dendritic Cells and Initiation of the Rejection Response 1017
48.3	Direct versus Indirect Pathways of Allorecognition 1020
48.4	Dendritic Cells and Tolerance Induction 1021
48.5	Mechanisms underlying Dendritic-cell-induced T-cell Tolerance 1022
48.6	Dendritic Cells and the Control of Organ Transplant Outcome 1026
48.6.1	Dendritic Cell Manipulation for Tolerance Induction: Specific Culture
	Conditions 1027
48.6.2	Dendritic Cell Manipulation for Tolerance Induction: Pharmacological
	Manipulation 1027
48.6.3	Dendritic Cell Manipulation for Tolerance Induction: Genetic
	Engineering 1028

Contents	
48.6.4	Use of Specific Dendritic Cell Subsets for Tolerance Induction 1029
48.6.5	Dendritic Cell Therapy: Targeting the Indirect Pathway 1031
48.6.6	Dendritic Cells and the Treatment of Chronic Rejection 1033
48.7	Dendritic Cells and Cellular Markers of Transplant Tolerance 1034
48.8	Toward Clinical Use of Dendritic-cell-based Therapies for Tolerance
	Induction: Critical Considerations and Future Challenges 1035
48.8.1	Dendritic Cell–T Cell Interaction 1035
48.8.2	Dendritic Cells and Treg: a Complex Inter-relationship 1036
48.8.3	Fingerprints of "Tolerogenic" Dendritic Cells 1037
48.8.4	Dendritic Cells at the Crossroads of the Immune System 1037
48.9	Conclusions 1038
	Acknowledgments 1038
	References 1039
XVII	Allergy, Asthma 1047
49	Nickel Presentation to T Cells in Contact Hypersensitivity 1047
	H. U. Weltzien, K. Gamerdinger and HJ. Thierse
49.1	Introduction 1047
49.2	Molecular Basis of Nickel Presentation to Human T Cells 1048
49.2.1	CD4-positive T Cells 1048
49.2.2	CD8-positive T Cells and Non-HLA Restricted Nickel
	Presentation 1051
49.3	Nickel-Binding Proteins 1051
49.3.1	A Role for Carrier Proteins in Nickel Presentation 1051
49.3.2	Heatshock Proteins as Nickel Binders 1052
49.4	Concluding Remarks 1053
	References 1055
50	Dendritic Cells in Asthma 1059
	Hamida Hammad and Bart N. Lambrecht
50.1	Introduction 1059
50.2	Asthma as a Th2 Driven Disorder 1059
50.3	Lung Dendritic Cell Subsets 1061
50.4	Function of Lung Dendritic Cells in Primary Immune Responses to
	Inhaled Antigen and Sensitization to Inhaled Allergen 1062
50.5	Is Tolerance Induction in the Lung a Property of Specialized Dendritic
	Cell Subsets? 1065
50.6	Accumulation of Mature Dendritic Cells in Ongoing Asthmatic
	Inflammation 1066
50.7	Direct Proof for a Functional Role for Dendritic Cells in Stimulating
	Effector Th2 Responses 1068
50.8	Determinants of Dendritic Cell Driven Th2 Responses in Asthma 1069
50.9	Dendritic Cells in Human Asthma 1071
50.10	Conclusion 1072

References 1073

XXXIV

XVIII	Cancer 1081
51	Dendritic Cells in Human Cancer 1081
	Casey A. Carlos and Olivera J. Finn
51.1	Introduction 1081
51.2	Dendritic Cell Functions that are Important for Effective Immunity against Cancer 1082
51.3	Dendritic Cell Recognition of Malignant Changes in Tissues 1083
51.4	How Tumors Interfere with Normal Dendritic Cell Function 1084
51.4.1	Inhibition of Maturation and Differentiation 1084
51.4.2	Influence on Migration 1085
51.4.3	Suppression of Function 1086
51.5	Summary 1087
	References 1088
Part C	Therapeutical Applications of Dendritic Cells 1093
XIX	Cancer 1095
52	Dendritic Cell Subsets as Targets and Vectors for Vaccination 1095
	Hideki Ueno, Joseph Fay, Jacques Banchereau and A. Karolina Paluck
52.1	Introduction 1095
52.2	Cancer Vaccines 1096
52.3	Dendritic Cells 1097
52.3.1	Dendritic Cell Subsets 1097
52.3.2	Distinct Dendritic Cell Subsets Induce Distinct Types of Immune
	Response 1099
52.3.3	Dendritic Cells and Immune Tolerance 1100
52.4	Dendritic Cells as Cancer Vaccines 1100
52.4.1	Dendritic Cell Subsets 1100
52.4.2	Dendritic Cell Maturation 1101
52.4.3	Dendritic Cell Migration 1102
52.4.4	Antigen Loading 1103
52.5	Regulatory/suppressor Mechanisms 1104
52.6	Immunological and Clinical Efficacy 1105
52.6.1	Immunological Efficacy 1105
52.6.2	Clinical Efficacy 1106
52.7	Conclusions 1107
	Acknowledgements 1107
	References 1107

IVXX	Contents

53	Renal Cell Carcinoma 1117
	Martin Thurnher, Thomas Putz, Andrea Rahm, Hubert Gander,
	Reinhold Ramoner, Georg Bartsch, Lorenz Höltl and
	Claudia Falkensammer
53.1	Dendritic Cells and Cancer Immunosurveillance 1117
53.2	Renal Cell Carcinoma 1117
53.3	Immunotherapy of Renal Cell Carcinoma 1118
53.4	Dendritic Cell-based Immunotherapy of Renal Cell Carcinoma 1119
53.4.1	The Two-step Culture System 1119
53.4.2	Generation of Clinical Grade Dendritic Cells 1119
53.4.3	Clinical Trials of Dendritic Cells in Renal Cell Carcinoma Patients 1120
53.5	Adjuvant Immunotherapy of Organ Confined Renal Cell Carcinoma after Partial or Radical Nephrectomy 1122
53.6	Patient Selection in Future Trials 1123
53.7	Adverse Effects – Quality of Life 1123
53.8	Concluding Remarks 1124
	Acknowledgements 1124
	References 1124
XX	Antigen Delivery 1129
54	Crosspresentation and Loading of Tumor Antigens for Dendritic Cell
54	Crosspresentation and Loading of Tumor Antigens for Dendritic Cell Vaccination against Cancer 1129
54	
54 .1	Vaccination against Cancer 1129
	Vaccination against Cancer 1129 Madhav V. Dhodapkar
	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129
54.1	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129
54.1 54.2	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130 Uptake of Dying Cells 1131
54.1 54.2 54.3	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130
54.1 54.2 54.3	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130 Uptake of Dying Cells 1131 Uptake of Immune Complexes and Opsonized Pathogens and Tumor
54.1 54.2 54.3 54.4 54.5 54.6	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130 Uptake of Dying Cells 1131 Uptake of Immune Complexes and Opsonized Pathogens and Tumor Cells 1131
54.1 54.2 54.3 54.4 54.5	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130 Uptake of Dying Cells 1131 Uptake of Immune Complexes and Opsonized Pathogens and Tumor Cells 1131 Uptake of Heat Shock Protein–Peptide Complexes 1132 Exosomes as Sources of Multiple Tumor Antigens 1133 Role of C-type Lectin Receptors 1133
54.1 54.2 54.3 54.4 54.5 54.6	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130 Uptake of Dying Cells 1131 Uptake of Immune Complexes and Opsonized Pathogens and Tumor Cells 1131 Uptake of Heat Shock Protein–Peptide Complexes 1132 Exosomes as Sources of Multiple Tumor Antigens 1133 Role of C-type Lectin Receptors 1133
54.1 54.2 54.3 54.4 54.5 54.6 54.7	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130 Uptake of Dying Cells 1131 Uptake of Immune Complexes and Opsonized Pathogens and Tumor Cells 1131 Uptake of Heat Shock Protein–Peptide Complexes 1132 Exosomes as Sources of Multiple Tumor Antigens 1133 Role of C-type Lectin Receptors 1133
54.1 54.2 54.3 54.4 54.5 54.6 54.7 54.8	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130 Uptake of Dying Cells 1131 Uptake of Immune Complexes and Opsonized Pathogens and Tumor Cells 1131 Uptake of Heat Shock Protein–Peptide Complexes 1132 Exosomes as Sources of Multiple Tumor Antigens 1133 Role of C-type Lectin Receptors 1133 Other Routes of Antigen Entry for Crosspresentation 1133 Processing of the Antigenic Cargo 1134 Nature of the Antigenic Cargo 1134
54.1 54.2 54.3 54.4 54.5 54.6 54.7 54.8 54.9	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130 Uptake of Dying Cells 1131 Uptake of Immune Complexes and Opsonized Pathogens and Tumor Cells 1131 Uptake of Heat Shock Protein–Peptide Complexes 1132 Exosomes as Sources of Multiple Tumor Antigens 1133 Role of C-type Lectin Receptors 1133 Other Routes of Antigen Entry for Crosspresentation 1133 Processing of the Antigenic Cargo 1134 Nature of the Antigenic Cargo 1134
54.1 54.2 54.3 54.4 54.5 54.6 54.7 54.8 54.9 54.10	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130 Uptake of Dying Cells 1131 Uptake of Immune Complexes and Opsonized Pathogens and Tumor Cells 1131 Uptake of Heat Shock Protein–Peptide Complexes 1132 Exosomes as Sources of Multiple Tumor Antigens 1133 Role of C-type Lectin Receptors 1133 Other Routes of Antigen Entry for Crosspresentation 1133 Processing of the Antigenic Cargo 1134 Nature of the Antigenic Cargo 1134
54.1 54.2 54.3 54.4 54.5 54.6 54.7 54.8 54.9 54.10 54.11	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130 Uptake of Dying Cells 1131 Uptake of Immune Complexes and Opsonized Pathogens and Tumor Cells 1131 Uptake of Heat Shock Protein-Peptide Complexes 1132 Exosomes as Sources of Multiple Tumor Antigens 1133 Role of C-type Lectin Receptors 1133 Other Routes of Antigen Entry for Crosspresentation 1133 Processing of the Antigenic Cargo 1134 Nature of the Antigenic Cargo 1134 Regulation of Crosspresentation during Dendritic Cell Maturation 1135 Role of Dendritic Cell Subsets in Crosspresentation 1136 Some Approaches to Improve Antigen Loading of Dendritic Cells for
54.1 54.2 54.3 54.4 54.5 54.6 54.7 54.8 54.9 54.10 54.11 54.12	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130 Uptake of Dying Cells 1131 Uptake of Immune Complexes and Opsonized Pathogens and Tumor Cells 1131 Uptake of Heat Shock Protein–Peptide Complexes 1132 Exosomes as Sources of Multiple Tumor Antigens 1133 Role of C-type Lectin Receptors 1133 Other Routes of Antigen Entry for Crosspresentation 1133 Processing of the Antigenic Cargo 1134 Nature of the Antigenic Cargo 1134 Regulation of Crosspresentation during Dendritic Cell Maturation 1135 Role of Dendritic Cell Subsets in Crosspresentation 1136
54.1 54.2 54.3 54.4 54.5 54.6 54.7 54.8 54.9 54.10 54.11 54.12	Vaccination against Cancer 1129 Madhav V. Dhodapkar Approaches to Antigen Loading for Dendritic-cell-mediated Immunotherapy 1129 Importance of Receptor-mediated Uptake to Crosspresentation 1130 Uptake of Dying Cells 1131 Uptake of Immune Complexes and Opsonized Pathogens and Tumor Cells 1131 Uptake of Heat Shock Protein-Peptide Complexes 1132 Exosomes as Sources of Multiple Tumor Antigens 1133 Role of C-type Lectin Receptors 1133 Other Routes of Antigen Entry for Crosspresentation 1133 Processing of the Antigenic Cargo 1134 Nature of the Antigenic Cargo 1134 Regulation of Crosspresentation during Dendritic Cell Maturation 1135 Role of Dendritic Cell Subsets in Crosspresentation 1136 Some Approaches to Improve Antigen Loading of Dendritic Cells for

55	Nucleic Acid Transfer 1143
	Niels Schaft, Jan Dörrie and Dirk M. Nettelbeck
55.1	General Introduction 1143
55.2	Antigen Delivery to DC by Adenoviral Gene Transfer 1145
55.2.1	Recombinant Adenovirus as Gene Transfer Vector 1146
55.2.2	Adenoviral Gene Transfer into Dendritic Cells in Vitro 1149
55.2.3	Adenoviral Antigen Delivery to DC for Ex Vivo Tumor Vaccination in
	Mouse Tumor Models 1151
55.2.4	Adenoviral Ag Delivery for HIV/SIV Vaccination in Monkeys 1153
55.3	Antigen Delivery to DC by Transfection of Nucleic Acids 1154
55.3.1	Passive Pulsing 1155
55.3.2	Electroporation 1156
55.3.3	Lipofection 1159
55.4	Concluding Remarks 1160
	References 1161

Subject Index 1173