Contents

Contributors xi

p	A	E	2	г	I:	PI	21	IN	10	F	T	F	S	1	7	F	C	Δ	. 7	V	C	F	R	T	N	1	M	П	11	V	C	F	13	C	T	C	10	27	v
	_					 			м,	_			o				•	-4			•		n		1.4				31		•	,	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		,	٠.	٠.	ж.	

	ntroduction 3 George C. Prendergast and Elizabeth M. Jaffee
I.	Overview 3
II.	Historical Background 3
	Looking Ahead: Marrying Chemotherapy and Immunotherapy 5 Parts of the Book 6
	References 8
	Further Reading 8
	Cancer Immunoediting: From Immune Surveillance to Immune Escape Ryungsa Kim
L	Introduction 10
II.	Cancer Immune Surveillance 10
III.	Cancer Immunoediting 19
IV.	Concluding Remarks 25
	References 25
	mmunosurveillance: Innate and Adaptive Antitumor Immunity 29 Masahisa Jinushi and Glenn Dranoff
L	Introduction 30
II.	Innate Antitumor Responses 30
III.	Innate Immune Cells 31
IV.	Adaptive Antitumor Responses 33
	The Interplay of Innate and Adaptive Antitumor Immunity 38
V.	
V. VI.	Conclusion 39

9

- I. Introduction 43
- II. Cytokine Regulation of Immune Tolerance to Tumors 45
- III. Summary and Future Perspectives 55 References 56

vi CONTENTS

Immunological Sculpting: Natural Killer Cell Receptors and Ligands 63 David A. Sallman and Julie Y. Djeu

- I. Introduction 64
- II. Activating Human NK Receptors 65
- III. Inhibitory NK Receptors 72
- IV. The Ly49 Receptor Family 74
- V. Immunotherapy Approaches 74
- VI. Conclusion 77 References 78 Further Reading 80

Immune Escape: Immunosuppressive Networks 83 Shuang Wei, Alfred Chang, and Weiping Zou

- I. Introduction 83
- II. Imbalance Between Mature DCs and Immature DCs 84
- III. Imbalance Between Stimulatory and Inhibitory B7 Family Molecules 87
- IV. Imbalance Between Regulatory T Cells and Conventional T Cells 90
- V. Concluding Remarks 92 References 92

PART II: CANCER THERAPEUTICS

Cytotoxic Chemotherapy in Clinical Treatment of Cancer 101 Rajesh Thirumaran, George C. Prendergast, and Paul B. Gilman

- I. Introduction 101
- II. DNA-Damaging Agents 103
- III. Antimetabolites 109
- IV. Antimitotics 112
- V. Chemotherapy Regimens 113 References 115 Useful Web Sites 116

8. Targeted Therapeutics in Cancer Treatment 117 Colin D. Weekes and Manuel Hidalgo

- I. Introduction 118
- II. Cell Cycle 119
- III. The MAPK Family 131
- IV. Challenges in the Clinical Development of Signal Transduction Inhibitors 136 References 140

9. Concepts in Pharmacology and Toxicology 149 Richard A. Westhouse and Bruce D. Car

- I. Introduction 150
- II. Concepts in Pharmacokinetics 151
- III. Concepts in Toxicology 159

CONTENTS vii

IV.	Clinical Concerns for Pharmacology and Safety	164
V.	Conclusion 165	

References 165 Further Reading 166

Cancer Immunotherapy: Challenges and Opportunities 167 Andrew J. Lepisto, John R. McKolanis, and Olivera J. Finn

I. Introduction 168

- II. Prerequisites for Effective Cancer Immunotherapy: Identifying Tumor Antigens 168
- III. Adoptive ("Passive") Immunotherapy 169
- IV. Active-Specific Immunotherapy: Vaccines 171
- V. Cancer-Induced Immunosuppression Impinges on Immunotherapy 172
- VI. Cancer Immunotherapy in Mice Versus Humans 175
- VII. Immunotherapy and Cancer Stem Cells 176
- VIII. Autoimmunity Resulting from Cancer Immunotherapy 176
- IX. Conclusion and Future Considerations 177 References 178

11. Cancer Vaccines 183

Freda K. Stevenson, Gianfranco Di Genova, Christian Ottensmeier, and Natalia Savelyeva

- I. Introduction 184
- II. Tumor Antigens 185
- III. Spontaneous Immunity to Cancer 187
- IV. Toleragenic Pressure on Immunity to Cancer 187
- V. Immune Responses to Conventional Vaccines 189
- VI. Cancer Vaccine Strategies 194
- VII. DNA Vaccines 195
- VIII. Challenges of Translation to the Clinic 199
- IX. Concluding Remarks 200 References 200
 - Further Reading 204

PART III: TARGETS AND TACTICS TO IMPROVE CANCER IMMUNOTHERAPY BY DEFEATING IMMUNE SUPPRESSION

12. Immunotherapy and Cancer Therapeutics: Why Partner? 207

Leisha A. Emens and Elizabeth M. Jaffee

- I. Introduction: Why Immunotherapy for Cancer? 208
- II. Immune Tolerance and Suppression: Multiple Layers of Negative Control 209
- III. T Cell Activation: A Rheostat for Tuning Immune Responses 212
- IV. Immune Modulation with Therapeutic Monoclonal Antibodies 219
- V. Therapeutics that Mitigate the Influence of CD4 CD25 Tregs 222
- VI. Endocrine and Biologically Targeted Therapy 224
- VII. Conclusion 225 References 225

viii CONTENTS

13.	Immune Stimulatory Features of Classical Chemotherapy	235
	Robbert G. van der Most, Anna K. Nowak, and Richard A. Lake	

- I. Introduction 236
- II. Tumor Cell Death 236
- III. Pathways to Immunogenicity 239
- IV. Chemotherapy and the Immune System 243
- V. A Practical Partnership: Chemotherapy and Immunotherapy 246
- VI. Effects of Chemotherapy on Human Antitumor Immunity and Chemoimmunotherapy Clinical Trials 250 References 252

Dendritic Cells and Coregulatory Signals: Immune Checkpoint Blockade to Stimulate Immunotherapy 257

Drew Pardoll

- I. Regulation of T Cell Responses to Antigen 258
- II. Regulatory T Cells 261
- III. Immune Checkpoints in the Tumor Microenvironment 262
- IV. Monoclonal Antibodies that Interfere with Coinhibitory Receptors on T Cells 266
- V. What Is the Most Effective Way to Use Checkpoint Inhibitors? 269 References 270

Regulatory T Cells in Tumor Immunity: Role of Toll-Like Receptors 277 Rong-Fu Wang

- I. Introduction 278
- II. Immune Cells in Immunosurveillance and Tumor Destruction 278
- III. TLRs and Their Signaling Pathways 279
- IV. TLRs in Innate Immunity, Inflammation, and Cancer Development 280
- V. Tumor-Infiltrating Immune Cells in the Tumor Microenvironment 281
- VI. Molecular Marker for CD4* Tregs 28.
- VII. Antigen Specificity of CD4⁺ Tregs 282
- VIII. Suppressive Mechanisms of Tregs 283
- IX. Functional Regulation of Tregs and Effector Cells by TLR Signaling 283
- X. Implications for Enhancing Antitumor Immunity 284
- XI. Conclusion 285 References 285

Tumor-Associated Macrophages in Cancer Growth and Progression 289 Alberto Mantovani, Paola Allavena, and Antonio Sica

- I. Introduction 289
- II. Macrophage Polarization 290
- III. Macrophage Recruitment at the Tumor Site 291
- IV. Tam Expression of Selected M2 Protumoral Functions 294
- V. Modulation of Adaptive Immunity by Tams 296
- VI. Targeting Tams 297
- VII. Concluding Remarks 300 References 302

CONTENTS ix

17. Tumor-Associated Myeloid-Derived Suppressor Cells 309

Stephanie K. Bunt, Erica M. Hanson, Pratima Sinha, Minu K. Srivastava, Virginia K. Clements, and Suzanne Ostrand-Rosenberg

- I. Introduction 310
- II. Multiple Suppressive Mechanisms that Contribute to Immunosuppression in Individuals with Tumors 310
- III. MDSCs as a Key Cell Population that Mediates Tumor-Induced Immunosuppression 311
- IV. MDSCs' Use of Mechanisms to Mediate Effects on Multiple Target Cells 317
- V. MDSC Induction by Tumor-Derived Cytokines and Growth Factors 321
- VI. MDSC Linking of Inflammation and Tumor Progression 322
- VII. Agents Responsible for Reducing MDSC Levels 323
- VIII. Conclusions: Implications for Immunotherapy 326 References 327

Further Reading 331

Programmed Death Ligand-1 and Galectin-1: Pieces in the Puzzle of Tumor-Immune Escape 333

Gabriel A. Rabinovich and Thomas F. Gajewski

- Programmed Death Ligand 1 and Programmed Death 1 Interactions 334
- II. Galectin 1 338 References 344

Further Reading 346

Indoleamine 2,3-Dioxygenase in Immune Escape: Regulation and Therapeutic Inhibition 347

Alexander J. Muller and George C. Prendergast

- I. Introduction 348
- II. IDO Function in T Cell Regulation 351
- III. Complex Control of IDO by Immune Regulatory Factors 351
- IV. Immune Tolerance Via IDO in Dendritic Cells 353
- V. IDO Dysregulation in Cancer Cells 357
- VI. IDO as a Target for Therapeutic Intervention 359
- VII. Discovery and Development of IDO Inhibitors 360
- VIII. Conclusion 361 References 362

Further Reading 368

Arginase, Nitric Oxide Synthase, and Novel Inhibitors of L-Arginine Metabolism in Immune Modulation 369

Susanna Mandruzzato, Simone Mocellin, and Vincenzo Bronte

- L Introduction 370
- II. NOS: Genes, Regulation, and Activity 371
- III. ARG: Genes, Regulation, and Activity 372
- IV. Immunoregulatory Activities of ARG and NOS 374
- V. Possible Physiological Role for L-ARG Metabolism in Immunity Control 381
- VI. NOS in Cancer 382

X CONTENTS

VII. ARG in Cancer 384

VIII. ARG and NOS Inhibitors: A Novel Class of Immune Adjuvants? 386

IX. Conclusion and Perspectives 388

References 389

Further Reading 399

Index 401