

## Contents

### Volume 1

#### Preface

#### Part I Death Receptor

- 1 The role of CD95/CD95 Ligand Signaling in Apoptosis and Cancer** 3  
*Karsten Gülow, Marcin Kamiński and Peter H. Kramer*
- 1.1 Introduction 3
- 1.1.1 The Apoptotic Machinery 4
- 1.1.2 The Intrinsic Pathway – Mitochondrial Involvement in Apoptosis 4
- 1.1.3 The Extrinsic Pathway – The Role of Death Receptors and their Ligands 5
- 1.1.4 The CD95 System 7
- 1.1.5 The Two-pathways Model for CD95 Signaling 8
- 1.1.6 The Death Ligand – CD95L 10
- 1.2 Cancer and Apoptosis 13
- 1.2.1 Resistance Mechanisms – Expression of Antiapoptotic Proteins 13
- 1.2.2 Resistance Mechanisms – Inactivation of Proapoptotic Genes 14
- 1.3 Cancer and CD95/CD95L System 14
- 1.3.1 Resistance Mechanisms – Mutations and Reduced Expression of CD95/CD95L 14
- 1.3.2 Resistance Mechanisms – Induction of CD95/CD95L Signaling 16
- 1.3.3 The CD95/CD95L System and Cancer Therapy 17
- 2 The TRAIL Receptor–Ligand System: Biochemistry of Apoptosis Induction, Therapeutic Potential for Cancer Treatment and Physiological Function** 31  
*Henning Walczak, Ronald Koschny, Daniela Willen, Manuela B. Schader, Jaromir Sykora, Tom M. Ganten and Tobias L. Haas*
- 2.1 Introduction 31
- 2.2 The TRAIL–TRAIL-Receptor System 33
- 2.2.1 TRAIL 33
- 2.2.2 The TRAIL-Receptors 33

2.2.3	TRAIL-induced Signaling	36
2.3	TRAIL in Cancer Therapy – Clinical Applications and Safety	45
2.3.1	Expression of TRAIL and its Receptors	45
2.3.2	Efficacy and Safety of Soluble Recombinant TRAIL	49
2.3.3	Agonistic TRAIL-R1- and TRAIL-R2-specific Monoclonal Antibodies	52
2.3.4	TRAIL Gene Therapy	54
2.3.5	Tumor-specific TRAIL Sensitization by Combinatorial Therapy	55
2.4	The Physiological Role of the TRAIL System	61
2.4.1	TRAIL and T cells	62
2.4.2	TRAIL and Immune Surveillance of Cancer	63
2.4.3	TRAIL and Viral Infections	66
2.4.4	Role of TRAIL in Immunopathologies, Autoimmune Diseases and Negative Selection	69
2.4.5	TRAIL in Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)	71
2.5	Concluding Remarks	74
<b>3</b>	<b>Mechanisms of Tumor Necrosis Factor-induced Cell Death</b>	<b>93</b>
	<i>Harald Wajant</i>	
3.1	Introduction	93
3.1.1	The Tumor Necrosis Factor (TNF)–TNF Receptor (TNF-R) System	93
3.1.2	TNF-R1 and TNF-R2 Belong to Different Subgroups of the TNF Receptor Family	95
3.2	Mechanisms of TNF-R1-induced Apoptosis	96
3.2.1	TNF-R1 Triggers NF- $\kappa$ B Activation and Apoptosis Induction	96
3.2.2	TNF-R1 Induces Apoptosis by a Fas-associated Death Domain (FADD)- and Caspase-8-dependent Pathway	99
3.3	The Role of TNF-R2 in TNF-induced Apoptosis	104
3.3.1	Apoptotic TNF Receptor Crosstalk	104
3.3.2	TNF-R2-induced Apoptosis	106
3.4	TNF-induced Apoptosis and the JNK Pathway	107
3.4.1	TNF-induced NF- $\kappa$ B Signaling Interferes with Prolonged JNK Activation	107
3.4.2	Apoptosis Signaling Kinase 1 (ASK1) and its Role in TNF-induced JNK Signaling	108
3.4.3	Targets of Proapoptotic JNK Signaling	108
3.5	TNF-induced Necrosis	109
3.6	TNF in Tumor Therapy	112
<b>4</b>	<b>Cellular FLICE-inhibitory Protein: An Update</b>	<b>120</b>
	<i>Olivier Micheau</i>	
4.1	Introduction	120
4.2	Structure of c-FLIPs	121
4.3	c-FLIP Function	123
4.3.1	c-FLIP <sub>L</sub> – a caspase-8/-10 Inhibitor or Activator?	123

4.3.2	c-FLIP <sub>L</sub> immune and Nonimmune Functions	124
4.4	Regulation of c-FLIP Expression	129
4.5	c-FLIP and Human Diseases	130
4.6	c-FLIP and Cancer	140
4.7	Conclusions	142
<b>5</b>	<b>Dependence Receptors and Apoptosis</b>	<b>157</b>
	<i>Patrick Mehlen and Filipe Calheiros Lourenço</i>	
5.1	Dependence Receptors: Apoptosis when Unbound	157
5.1.1	p75 <sup>NTR</sup> : The First Dependence Receptor Described	159
5.1.2	The Putative Tumor Suppressor and Axon Guidance-related Receptor DCC	160
5.1.3	The Netrin-1 Receptor UNC5H	162
5.1.4	Neogenin: A DCC Homolog Joins the Family	162
5.1.5	RET: A Dependence Receptor Tyrosine Kinase (RTK)	163
5.1.6	Integrins as Dependence Receptors	163
5.1.7	Ptc: A 12-transmembrane Dependence Receptor	164
5.1.8	AR: A Nuclear Dependence Receptor	164
5.2	Dependence Receptors: To Get Caspase Amplification	165
5.3	Dependence Receptors: Patterning during Neural Development	170
5.4	Dependence Receptors: Conditional Tumor Suppressors	172
5.5	Concluding Remarks	179
<b>Part II</b>	<b>Mitochondria</b>	
<b>6</b>	<b>Role of Mitochondrial Proteins in Apoptosis</b>	<b>185</b>
	<i>Xavier Saelens, Nele Festjens, Lieselotte Vande Walle and Peter Vandennebeele</i>	
6.1	Introduction	186
6.2	Bcl-2 Family Proteins and Mitochondrial Membrane Permeabilization	187
6.3	Mutations in the Intrinsic Apoptotic Pathway Contributing to Cancer	189
6.4	Cytochrome <i>c</i>	190
6.5	Cytochrome <i>c</i> Release: A Point of No Return?	195
6.6	IAP Inhibition by Mitochondrial Proteins	197
6.6.1	Smac/DIABLO	197
6.6.2	HtrA2/OMI	201
6.6.3	ARTS	204
6.6.4	AIF	205
6.6.5	EndoG	208
6.7	Other Mitochondrial Factors Released During Apoptosis	209
6.8	Conclusions and Perspectives	210

<b>7</b>	<b>Omi/HtrA2: A Mitochondrial Serine Protease Regulating Cellular Life and Death</b> 222
	<i>Yasuyuki Suzuki and Ryosuke Takahashi</i>
7.1	Introduction 222
7.2	Structure and Properties of Omi/HtrA2 224
7.3	Cell Death Regulation by Omi/HtrA2 225
7.4	Omi/HtrA2 Mutant Mice 227
7.5	Omi/HtrA2 and Cancer Therapy 228
7.6	Conclusions 229
<b>8</b>	<b>Apoptosis-inducing Factor</b> 233
	<i>Nicola Vahsen and Guido Kroemer</i>
8.1	Introduction 233
8.2	AIF Expression, Structure and Localization 234
8.2.1	Isoforms 236
8.2.2	Nonmammalian Orthologs and Mammalian Homologs 237
8.3	The Apoptotic Function 238
8.3.1	Cell-free Systems 238
8.3.2	<i>In Vivo</i> 239
8.3.3	Downregulation of AIF 239
8.4	AIF Translocation 241
8.4.1	How is AIF Released? 241
8.4.2	Are Caspases Required? 243
8.4.3	When is AIF Released? 244
8.4.4	Hsp70 245
8.5	How Does AIF Exert its Effect on DNA? 246
8.5.1	EndoG 246
8.5.2	CypA 247
8.6	The Vital Functions 247
8.6.1	Radical Scavenger and/or Maintenance Factor in the Respiratory Chain 247
8.6.2	AIF and Cytoplasmic Stress Granules 248
8.6.3	AIF is a Bifunctional Protein 248
8.7	AIF in Disease 249
8.7.1	AIF and Cancer 249
8.7.2	AIF in Acute Cell Loss 249
8.7.3	AIF in Infectious Diseases 250
8.7.4	AIF in Neurodegenerative Diseases 250
8.8	Concluding Remarks 250

**Part III Effector Systems**

- 9 Caspases: Agents of Defense and Destruction 259**  
*Colin Adrain and Seamus J. Martin*
- 9.1 Introduction 259
- 9.2 Caspases: Ubiquitous Mediators of Apoptotic Cell Death...And More 260
- 9.3 Caspase Structure and Classification 262
- 9.4 Catalytic Properties of Caspases 263
- 9.5 Biochemical Mechanisms 265
- 9.5.1 Biochemical Mechanisms of Executioner Caspase Activation 265
- 9.5.2 Biochemical Mechanisms of Initiator Caspase Activation 266
- 9.6 Pathways to Caspase Activation 267
- 9.6.1 The Mitochondrial Apoptosome Pathway 267
- 9.6.2 Granzyme B-mediated Caspase Activation 269
- 9.6.3 DR-mediated Caspase Activation 269
- 9.6.4 The PIDDosome 269
- 9.6.5 The Inflammasome 269
- 9.7 Caspase Substrates 270
- 9.7.1 Amplification of Apoptosis by Activation of the Apoptosome Cascade: Role of Bid 270
- 9.7.2 Nuclear Changes during Apoptosis 271
- 9.7.3 Shutdown of Transcription, RNA Synthesis, Protein Synthesis and Protein Post-translational Modification 272
- 9.7.4 Shutdown of ATP-hydrolyzing Enzymes 272
- 9.7.5 Cell Rounding and Blebbing 272
- 9.8 Physiological Roles of Caspases in Apoptosis and Inflammation 273
- 9.8.1 Caspases and Apoptosis: Initiator Caspase-9 273
- 9.8.2 Caspases and Apoptosis: Initiator Caspase-2 274
- 9.8.3 Caspases and Apoptosis: Initiator Caspase-8 274
- 9.8.4 Primacy or Redundancy of Caspase-3 in Apoptotic Execution? 275
- 9.8.5 Physiological Roles of the Inflammatory Caspases 276
- 9.9 Deregulation of Caspases in Cancer 277
- 9.10 Harnessing Caspase Activation in Anticancer Therapy 278
- 10 The Role of the Apoptosome in Apoptosis and Cancer Therapy 282**  
*Kelvin Cain*
- 10.1 Introduction 283
- 10.2 Cytochrome *c*: The Intracellular Signal for Apoptosome Formation 285
- 10.3 Domains of Apaf-1: The Building Block of the Apoptosome 288
- 10.4 Activation of Apaf-1 and Apoptosome Formation Requires Adenine Nucleotides and Cytochrome *c* 290
- 10.5 Assembly and Composition of the Apoptosome 292
- 10.6 The Apoptosome Processes and Activates Caspase-9 and the Effector Caspases 294

- 10.7 Physiological Mechanisms that Regulate the Apoptosome 296
- 10.8 Apaf-1 and Apoptosome Function are Essential for Embryonic Development 298
- 10.9 The Role of the Apoptosome in Cancer Therapy 299
- 10.10 Apoptosome and Caspase-independent Cell Death 302
- 10.11 The Effect of Small Molecules on Apoptosome Formation and Function 303
- 10.12 Is the Apoptosome a Good Target for Cancer Therapy? 304

**Part IV Bcl-2 Family**

- 11 The Role of the Bcl-2 Protein Family in Tumorigenesis and Cancer Therapy 317**  
*Edwina Naik and Andreas Strasser*
- 11.1 Introduction 317
- 11.2 Tools of the Trade: The Cell Death Machinery 320
- 11.3 The Bcl-2 Family of Proteins 322
- 11.3.1 Prosurvival Bcl-2 Family Members 322
- 11.3.2 Multi-BH Domain Proapoptotic Bcl-2 Family Members are Essential for Apoptosis 325
- 11.3.3 BH3-only Proteins are Sensors of Cellular Stress Essential for Apoptosis Initiation 327
- 11.3.4 The Balance between Pro- and Antiapoptotic Bcl-2 Family Members Determines Cell Fate 330
- 11.3.5 Bcl-2 Family Members Function Downstream of Tumor Suppressor Pathways 331
- 11.4 Role of the Bcl-2 Protein Family Members in Tumorigenesis 332
- 11.4.1 Role of prosurvival Bcl-2 Family Members in Tumorigenesis 332
- 11.4.2 Contribution of Bax/Bak deregulation to tumorigenesis 334
- 11.4.3 Contribution of Loss of BH3-only Proteins to Tumorigenesis 334
- 11.5 Bcl-2 Family Members Regulate Apoptotic Responses to Anticancer Agents 335
- 11.6 Bcl-2 Family Members as Targets for Cancer Therapy 337
- 11.6.1 Antisense RNA Strategy 337
- 11.6.2 RNA-mediated Gene Silencing – The Small Interfering RNA (siRNA) approach 337
- 11.6.3 Translating Structural Knowledge to Rational Drug Design – Small-molecule Inhibitors and BH3 Mimetics 338
- 11.7 Conclusions and Future Directions 339
- 12 Bax, Bak and Bid: Key Mediators of Apoptosis 346**  
*Clare E. Dempsey, Darren L. Roberts and Caroline Dive*
- 12.1 The Intrinsic Pathway of Apoptosis 346
- 12.2 Mechanism of Mitochondrial Killing 347

- 12.3 The Bcl-2 Family 348
- 12.4 Multidomain Proapoptotic Proteins Bax and Bak 349
  - 12.4.1 Possible Redundancy of Bax/Bak-like Molecules 350
  - 12.4.2 Role of Bax in Mitochondrial Fission and Fusion 351
- 12.5 Release of Mitochondrial Cytochrome *c* by Bcl-2 Family Proteins 352
- 12.6 BH3-only Bcl-2 Proteins 353
  - 12.6.1 Multiplicity of BH3-only proteins 353
- 12.7 A BH3-only Protein, Bid, That Can Interact with Both Pro- and Antiapoptotic Proteins 354
- 12.8 Functional Interactions between BH3-only Proteins and Multidomain Bcl-2 Proteins 356
- 12.9 Regulation of Bid 357
- 12.10 The Physiological Role of Bid 358
- 12.11 Full-length Bid versus t<sub>l</sub>Bid 360
- 12.12 Mechanisms by which Bid Causes Cytochrome *c* Release 360
- 12.13 Are Mitochondria Actually Required for Apoptosis? 362
- 12.14 Bid, Bax and Bak – Localization and Function at other Intracellular Organelles 363
- 12.15 Splice Variants of Bax, Bak and Bid 364
- 12.16 Bax, Bak and Bid in Cancer 365
- 12.17 Therapeutic Opportunities 366
  
- 13 The BH3-only Proteins Puma and Noxa: Two Brothers in Arms 379**  
*Miriam Erlacher, Ewa M. Michalak, Andreas Strasser and Andreas Villunger*
  - 13.1 Introduction 379
    - 13.1.1 Regulation of p53 Function 380
    - 13.1.2 Cell Fate Decisions by p53 381
  - 13.2 p53 and Cell Death Signaling 382
    - 13.2.1 Death Receptor Signaling and p53 383
    - 13.2.2 p53 Induces Cell Death Mainly via Activation of the Bcl-2-regulated Cell Death Pathway 383
  - 13.3 Regulation of Expression and Function of Bcl-2 Family Members by p53 385
    - 13.3.1 Puma and Noxa: Two Brothers in Arms 385
    - 13.3.2 Molecular Mechanisms of Puma-induced Apoptosis 388
    - 13.3.3 Noxa/APR 389
    - 13.3.4 Molecular Mechanisms of Noxa-induced Cell Death 390
  - 13.4 Lessons from Animal Models – When the Cat is Away... 390
    - 13.4.1 Does p53-mediated Tumor Suppression Depend on Puma or Noxa? 392
    - 13.4.2 Is Loss of Puma or Noxa Selected for during Tumorigenesis in Humans? 394

**Part V IAPs**

- 14 Inhibitor of Apoptosis Proteins 405**  
*Martin Holcik*
- 14.1 Introduction 405
  - 14.2 Mechanism and Regulation of Apoptosis 406
    - 14.2.1 Apoptotic Pathways 406
    - 14.2.2 The IAP gene family 407
    - 14.2.3 The Mechanism of IAP Action 409
    - 14.2.4 The *In Vivo* Role of IAPs – Animal Studies 412
  - 14.3 Regulation of IAP s Expression and Function 412
    - 14.3.1 Translational Regulation of IAPs 412
    - 14.3.2 Regulation by IAP-interacting Proteins 414
    - 14.3.3 IAP RING-mediated Ubiquitylation 418
  - 14.4 The Role of IAPs in Cancer 419
    - 14.4.1 Targeting IAPs in Cancer – Proof of Principle Studies 420
    - 14.5 Concluding Remarks 421
- 15 Targeting the Survivin Pathway for Rational Cancer Therapy 427**  
*Dario C. Altieri*
- 15.1 Introduction – Apoptotic Pathways 427
  - 15.2 Survivin Structure–Function 428
  - 15.3 Role of Survivin in Cell Division 429
  - 15.4 Role of Survivin in Apoptosis Inhibition 431
  - 15.5 Translational Targeting of the Survivin Pathway in Cancer 433
  - 15.6 Concluding Remarks 435

**Part VI Survival Pathways**

- 16 Nuclear Factor- $\kappa$ B in Apoptosis and Tumorigenesis 445**  
*Florian R. Greten and Michael Karin*
- 16.1 Family Members 445
  - 16.2 Regulation by the I $\kappa$ B Kinase (IKK) Complex 446
  - 16.3 NF- $\kappa$ B and Regulation of Apoptosis 447
  - 16.4 Survival Mechanisms 449
  - 16.5 NF- $\kappa$ B in Tumorigenesis 452
  - 16.6 Lessons from *In Vivo* Studies using Genetic and Pharmacologic Tumor Models 453
  - 16.7 NF- $\kappa$ B as a Target for Tumor Therapy 456

<b>17</b>	<b>Cell Survival Signaling through Phosphoinositide 3-kinase and Protein Kinase B</b>	<b>462</b>
	<i>Michael P. Scheid and James R. Woodgett</i>	
17.1	Introduction	462
17.1.1	A Brief History	463
17.2	PKB: A Member of the “AGC” Kinase Subfamily	464
17.3	DNA-dependent Protein Kinase (DNA-PK) is a PKB Kinase	466
17.4	Mammalian Target of Rapamycin (mTOR) – Another PKB Kinase	467
17.5	Non-PIKK PKB regulators	469
17.5.1	Integrin-linked Kinase (ILK)	469
17.5.2	C-terminal Modulator Protein (CTMP)	469
17.5.3	TCL1	469
17.6	PKB Substrates Involved in Apoptosis	470
17.6.1	Cell Death Machinery	470
17.6.2	Transcription Factor Control	471
17.7	Cell Cycle Progression is Controlled by PI3K–PKB	473
17.7.1	Cell Cycle Inhibitors p21 <sup>Waf1/Cip1</sup> and p27 <sup>Kip1</sup>	473
17.7.2	MDM2	474
17.7.3	PKB is a Regulator of G <sub>2</sub> /M Phase Transition	475
17.8	PI3K–PKB Effects on Glucose Metabolism	475
17.8.1	Hexokinase	475
17.8.2	GSK-3	476
17.8.3	PKB, GSK-3 and the Wnt Pathway	477
17.9	PKB Inhibits Transforming Growth Factor (TGF)- $\beta$ Signaling	479
17.10	Death and Survival by PKB in Neuronal Pathologies	480
17.10.1	Huntingtin	480
17.10.2	Ataxin-1	481
17.11	Conclusions	481
<b>18</b>	<b>Survival Regulation by Ras and Raf</b>	<b>490</b>
	<i>H. C. A. Drexler, A. Galmiche, M. Hekman, S. Albert and U. R. Rapp</i>	
18.1	Introduction	490
18.2	Signaling Pathways Controlling Cell Survival	492
18.2.1	Ras-dependent Protection against Apoptosis	492
18.2.2	Survival Control by Raf Kinases	494
18.3	Conclusions	506

**Part VII Oncogenes/Tumor Suppressor Genes**

- 19 p53-mediated Apoptosis: A Multifaceted Story 517**  
*Daniel Speidel and Wolfgang Deppert*
- 19.1 Introduction 517
- 19.2 Proapoptotic p53 Signaling I: Transcriptional Activities 519
- 19.3 Proapoptotic p53 Signaling II: Nontranscriptional Activities 522
- 19.4 Integration of Transcriptional and Nontranscriptional Proapoptotic p53 Activities 524
- 19.5 Added Complexity: Antiapoptotic p53 Signaling 528
- 19.6 Integration of Anti- and Proapoptotic p53 Activities 529
- 19.7 Mutant p53 Signaling 530
- 19.8 Concluding Remarks 531
- 20 p73 Affects Cell Fate and Tumorigenesis 536**  
*Safaa Ramadan, Emre Sayan, Andrew Oberst, Anissa Chikh, Valentina Pietroni, Alessandro Rufini, Gerry Melino and Francesca Bernassola*
- 20.1 Introduction 536
- 20.2 Regulation of p73 Induction and Transcriptional Activation 538
- 20.2.1 Role of Post-translational Modifications 538
- 20.2.2 Changes in Subcellular Localization 539
- 20.2.3 p73 Protein Interactors and Regulators 540
- 20.3 Proapoptotic Mechanisms Elicited by p73 542
- 20.4 Role of p73 in Tumorigenesis 543
- 20.4.1 Disruption of the Balance between TAp73 and  $\Delta$ Np73 Isoforms as a Determinant of Cancer Development 543
- 20.4.2 Does the Internal Ribosome Entry Site (IRES)-dependent Translation of the p73 mRNA Lead to the Generation of a Transactivation-deficient p73 Protein? 545
- 21 RB and Cancer 551**  
*B. Nelson Chau, Jacqueline Bergseid and Jean Y. J. Wang*
- 21.1 Introduction 551
- 21.2 RB: A Tissue-specific Tumor-suppressor Gene 553
- 21.3 The RB Gene Product 554
- 21.4 Mechanism of Transcription Regulation by RB 556
- 21.5 Regulation of RB by Phosphorylation 556
- 21.6 Biological Functions of RB Deduced from Mouse Genetic Studies 557
- 21.6.1 RB and Terminal Differentiation 557
- 21.6.2 RB and Cell Cycle Exit 558
- 21.6.3 RB and Apoptosis 558
- 21.7 RB-negative Cancer Cells are Hypersensitive to Chemotherapeutics 559
- 21.8 Caspase-resistant RB Protects Against TNF-induced Apoptosis 560
- 21.9 Two Models for the Antiapoptotic Function of RB 560

- 21.10 Apoptotic Defects Accompany RB Loss in Tumor Development 561
- 21.11 Enhanced Phosphorylation of RB in Sporadic Cancer 562
- 21.12 Upregulation of RB in Sporadic Human Cancer Cells 562
- 21.13 Summary and Future Prospects 563

## Part VIII Modulators

- 22 Calcium Signaling in Apoptosis 571**  
*Sten Orrenius and Boris Zhivotovsky*
- 22.1 Introduction 571
- 22.2 Major Forms of Cell Death 572
- 22.3 The Regulation of Intracellular  $\text{Ca}^{2+}$  Compartmentalization 573
- 22.4 The ER,  $\text{Ca}^{2+}$  and Apoptosis 574
- 22.4.1 ER Stress 575
- 22.5 Mitochondria,  $\text{Ca}^{2+}$  and Apoptosis 577
- 22.5.1 Mechanisms of Mitochondrial Permeabilization during Apoptosis 578
- 22.5.2 Role of  $\text{Ca}^{2+}$ -Cardiolipin Interaction in Cytochrome  $c$  Release 580
- 22.6  $\text{Ca}^{2+}$ -activated Effector Mechanisms 580
- 22.6.1 Calcineurin 581
- 22.6.2 Nitric Oxide Synthase (NOS) 581
- 22.6.3 Endonucleases 581
- 22.6.4 Phospholipases 582
- 22.6.5 Transglutaminases 582
- 22.6.6 Proteases 582
- 22.7 Crosstalk between Caspases and Calpains in Regulation of Cell Death 583
- 22.8 Caspases, Calpain and Intracellular Ion Homeostasis 584
- 22.9 Effects of Bcl-2 Family Proteins on ER  $\text{Ca}^{2+}$  Storage 585
- 22.10  $\text{Ca}^{2+}$  and the Phagocytosis of Apoptotic Cells 586
- 22.10.1 CD31 587
- 22.11 Calcium and Apoptosis in Cancer Cells 587
- 22.12 Conclusions 588

## Part IX Lysosomes and Nonapoptotic Pathways

- 23 Lysosomes and Nonapoptotic Pathways 599**  
*Thomas Kirkegaard-Sørensen, Nicole Fehrenbacher, Mads Gyrd-Hansen and Marja Jäättelä*
- 23.1 Introduction 599
- 23.2 Lysosomal Hydrolases 600
- 23.3 Trafficking To and From the Lysosomes 600
- 23.3.1 The Endocytic Route 601
- 23.3.2 The Biosynthetic Route 602
- 23.3.3 Autophagic Route 603
- 23.3.4 Reformation of Lysosomes and Lysosomal Secretion 604

- 23.4 Lysosomal Involvement in PCD 604
  - 23.4.1 LMP and its Consequences 605
  - 23.4.2 LMP as a Trigger of the Mitochondrial Apoptosis Pathway 606
  - 23.4.3 Mitochondrion-independent Death Pathways Induced by LMP 608
  - 23.4.4 Caspase-dependent and -independent Signaling to LMP 608
  - 23.4.5 Cellular Defense Mechanisms against LMP and its Consequences 611
- 23.5 Altered Lysosomal Function in Cancer Cells 611
  - 23.5.1 Cathepsins as Mediators of Cancer Invasion and Angiogenesis 612
  - 23.5.2 Immortalization and Transformation Sensitize Cells to the Lysosomal Death Pathway 612
  - 23.5.3 Hsp70 – The Guardian of Cancer Cell Lysosomes? 614
  - 23.5.4 Lysosomes as Targets for Future Cancer Therapy 615

**Part X Phagocytosis/Clearance**

- 24 The Role of “Eat Me”, “Don’t Eat Me” and “Find Me” Signals for the Efficient Removal of Apoptotic Cells 625**  
*Kirsten Lauber and Sebastian Wesselborg*
  - 24.1 Introduction 625
  - 24.2 The Engulfment Synapse 626
    - 24.2.1 “Eat me” Signals, Bridging Proteins and Phagocyte Receptors 626
    - 24.2.2 “Don’t Eat Me” Signals 631
    - 24.2.3 “Find Me” Signals 632
  - 24.3 The Engulfment Machinery of *C. elegans* 633
  - 24.4 Postphagocytic Responses 636
  - 24.5 Apoptotic Cell Removal and Autoimmunity 637
  - 24.6 Triggering Apoptotic Cell Removal as a Novel Approach to Cancer Therapy 639
  - 24.7 Conclusions 639
- 25 Apoptotic Cell Clearance by Macrophages: Relevance to Tumor Pathogenesis 647**  
*Christopher D. Gregory and Andrew Devitt*
  - 25.1 Overview 647
  - 25.2 Mechanisms and Consequences of Macrophage-mediated Clearance of Apoptotic Cells in Tumors 648
    - 25.2.1 Evidence for Apoptotic Cell Clearance by Macrophages in the Tumor Microenvironment 649
    - 25.2.2 Interactions between Macrophages and Apoptotic Cells 650
    - 25.2.3 Macrophage Responses to Apoptotic Cells 655
  - 25.3 Relationships between Macrophages and Apoptotic Cells in Tumors 658
    - 25.3.1 Apoptosis and Oncogenesis 658
    - 25.3.2 Interplay between Tumor Cells and TAMs 658
    - 25.4 Hypothesis: Apoptosis as a Primary Oncogenic Event? 660

## Volume 2

### Part XI Model Systems

- 26 Mouse Models in Cancer Research** 671  
*Soyoung Lee and Clemens A. Schmitt*

### Part XII Molecular Diagnosis

- 27 Molecular Imaging in Cancer** 705  
*Mahaveer Swaroop Bhojani, Bharathi Laxman, Brian D. Ross and Alnawaz Rehemtulla*
- 28 Microarray-based Expression Profiling: From Technological Basics to Diagnostic Perspectives** 728  
*Yana V. Syagailo, Wlad Kusnezow and Jörg D. Hoheisel*

### Part XIII Cellular Stress, DNA Damage and Repair

- 29 Life and Death Decisions in Response to Stress** 757  
*Michael J. Pinkoski*
- 30 Hypoxia in Cancer** 777  
*Ester M. Hammond, Ioanna Papandreou and Amato J. Giaccia*
- 31 Apoptosis Induced by DNA-damaging Agents** 799  
*Bernd Kaina and Wynand Roos*
- 32 DNA Repair** 822  
*Michael Schrauder and Lisa Wiesmüller*

### Part XIV Molecular Targets and Therapeutics

- 33 Therapeutic Modulation of Apoptosis in Cancer Therapy** 849  
*Simone Fulda and Klaus-Michael Debatin*
- 34 Current Therapeutic Strategies Targeting Caspases in Disease** 862  
*Ute Fischer and Klaus Schulze-Osthoff*
- 35 Cancer Therapy by Reactivation of the p53 Apoptosis Pathway** 891  
*Helene Stridh, Vladimir J. N. Bykov, Galina Selivanova and Klas G. Wiman*
- 36 Small-molecule Inhibitors of the Inhibitor of Apoptosis Proteins** 913  
*Robert C. Armstrong, Barbara A. Belli and Thomas L. Deckwerth*

- 37 Inhibition of the Molecular Chaperone Heat Shock Protein 90 in Cancer: Consequences for the Regulation of Survival Signaling and Induction of Cell Death** 933  
*Paul Andrew Clarke, Marissa Powers and Paul Workman*
- 38 Targeting the Phosphoinositide-3-kinase/Akt/Mammalian Target of Rapamycin Pathway** 966  
*Courtney A. Granville, Regan M. Memmott, Joell J. Gills and Phillip A. Dennis*
- 39 Ceramide Signaling in Apoptosis and Cancer Therapy** 997  
*Silke Kullmann, Volker Teichgräber, Claudia R. Bollinger and Erich Gulbins*
- 40 Histone Deacetylase Inhibitors: Development as Anticancer Agents** 1014  
*Paul A. Marks*
- 41 Exploiting Apoptosis Pathways for Glioblastoma Therapy** 1033  
*Johannes Rieger and Michael Weller*
- 42 Radiation Therapy and Apoptosis** 1049  
*Verena Jendrossek and Claus Belka*
- 43 Tumor Angiogenesis** 1087  
*Jürgen Becker, Jörg Wilting and Lothar L. Schweigerer*
- Index** 1107