

## Contents

	<b>Preface</b>	<i>XV</i>
	<b>Acknowledgments</b>	<i>XXI</i>
	<b>List of Abbreviations</b>	<i>XXIII</i>
	<b>About the Companion Website</b>	<i>XXIX</i>
<b>1</b>	<b>General Aspects of Signal Transduction and Cancer Therapy</b>	<b>1</b>
1.1	General Principles of Signal Transduction	2
1.1.1	Biological Signals have to be Processed	2
1.1.2	What is a Signal Transduction Pathway?	2
1.1.3	Mechanisms of Direct Signal Transduction	4
1.1.4	The Interactome Gives Insight into the Signaling Network	5
1.1.5	Protein Domains for Protein–Protein Interaction and Signal Transduction	6
1.1.6	Functions of Mutated Proteins in Tumor Cells	8
1.2	Drugs against Cancer	10
1.2.1	Terms and Definitions	10
1.2.2	The Steps from a Normal Cell to a Tumor	10
1.2.3	Interference Levels of Therapeutic Drugs	11
1.2.4	Drugs Attacking the Whole Cell	12
1.2.4.1	DNA Alkylating Drugs	13
1.2.5	Process-Blocking Drugs	14
1.2.5.1	Drugs Blocking Synthesis of DNA and RNA	14
1.2.5.2	Drugs Blocking the Synthesis of DNA and RNA Precursor Molecules	15
1.2.5.3	Drugs Blocking Dynamics of Microtubules	16
1.2.6	Innovative Molecule-Interfering Drugs	18
1.2.7	Fast-Dividing Normal Cells and Slowly Dividing Tumor Cells: Side Effects and Relapse	19
1.2.8	Drug Resistance	19
1.2.8.1	Drugs Circumventing Resistance	19
1.3	Outlook	20
	References	21

<b>2</b>	<b>Tumor Cell Heterogeneity and Resistance to Targeted Therapy</b>	<b>23</b>
2.1	The Genetic Basis of Tumorigenesis	24
2.2	Clonal Heterogeneity	24
2.2.1	Clonal Origin of Tumors	24
2.2.2	Clonal Evolution	26
2.2.3	The Time Course of Clonal Evolution	30
2.2.4	Clonal Evolution and Resistance to Therapy	32
2.2.5	Targeting Essential Drivers (Driver Addiction)	34
2.2.6	Resistance by Alternative Pathway Activation	36
2.2.7	Overcoming Resistance by Combinatorial Therapies	36
2.3	Tumor Stem Cells and Tumor Cell Hierarchies	37
2.4	Epigenetics and Phenotypic Plasticity	40
2.5	Microenvironment	42
2.6	Outlook	43
	References	44
<b>3</b>	<b>Cell Cycle of Tumor Cells</b>	<b>47</b>
3.1	Properties of Tumor Cells	48
3.1.1	Differences between Tumor Cells and Normal Cells In vitro	49
3.1.2	Regulation of Cell Number	49
3.2	The Cell Cycle	50
3.2.1	Checkpoints	51
3.2.2	Cyclins	52
3.2.3	Cyclin-Dependent Kinases (CDKs)	53
3.2.4	The Retinoblastoma-Associated Protein Rb as Regulator of the Cell Cycle	54
3.2.5	Inhibitors of CDKs	54
3.2.6	Checkpoints and DNA Integrity	55
3.2.7	The Repair Mechanism Depends on the Cell Cycle Phase	57
3.2.8	Tumor-Relevant Proteins in the Cell Cycle	57
3.3	The Cell Cycle as Therapeutic Target	58
3.3.1	Small Compounds Inhibiting Cell-Cycle-Dependent Kinases as Anticancer Drugs	59
3.4	Outlook	60
	References	61
<b>4</b>	<b>Cell Aging and Cell Death</b>	<b>63</b>
4.1	A Cell's Journey through Life	64
4.2	Cellular Aging and Senescence	64
4.2.1	Replicative Senescence	65
4.2.2	Shortening of Chromosomal Telomeres during Replication	67
4.2.3	Chromosomal Telomeres	67
4.2.4	Telomerase	69
4.2.5	Animal Models	72

4.2.6	Overcoming Replicative Senescence in Tumor Cells	72
4.2.7	Nonreplicative Senescence	73
4.3	Cell Death	74
4.4	Morphologies of Dying Cells	75
4.4.1	Morphology of Necrotic Cells	75
4.4.2	Morphologies of Apoptotic and Necroptotic Cells	75
4.4.3	Morphology of Autophagy	76
4.5	Necroptosis	76
4.6	Apoptosis in the Healthy Organism	79
4.6.1	The Four Phases of Apoptosis	80
4.6.2	Extrinsic Initiation	81
4.6.2.1	TNF Pathway	81
4.6.2.2	TNF Receptor Downstream Signaling	82
4.6.2.3	Caspases	82
4.6.3	Intrinsic Initiation	83
4.6.4	Execution Phase	84
4.6.5	Phagocytosis and Degradation	85
4.7	Apoptosis of Tumor Cells	85
4.8	Autophagy	86
4.8.1	Autophagy in Tumor Development	87
4.8.2	Regulation of Autophagy	89
4.9	Cell Death and Cell Aging as Therapeutic Targets in Cancer Treatment	89
4.9.1	Induction of Apoptosis by Radiation	89
4.9.2	Induction of Apoptosis by Conventional Anticancer Drugs	90
4.9.3	Innovative Drugs Targeting Aging and Death Pathways	92
4.9.3.1	Targeting TRAIL (TNF-Related Apoptosis-Inducing Ligand)	92
4.9.3.2	Targeting Bcl-2	92
4.9.3.3	Simulating the Effects of cIAP Inhibitors	92
4.9.3.4	Targeting Autophagy Pathways	93
4.10	Senescence in Anticancer Therapy	93
4.11	Outlook	94
	References	95
<b>5</b>	<b>Growth Factors and Receptor Tyrosine Kinases</b>	<b>97</b>
5.1	Growth Factors	98
5.2	Protein Kinases	98
5.2.1	Receptor Protein Tyrosine Kinases	100
5.2.2	Receptor Protein Tyrosine Kinase Activation	102
5.2.3	The Family of EGF Receptors	103
5.2.4	The Family of PDGF Receptors	104
5.2.5	The Insulin Receptor Family and its Ligands	107
5.2.5.1	Prostate-Specific Antigen	107
5.2.6	Signaling from Receptor Protein Tyrosine Kinases	108

5.2.7	Association of PDGF and EGF Receptors with Cytoplasmic Proteins 109
5.2.7.1	Signaling from PDGF and EGF Receptors 112
5.2.8	Constitutive Activation of RTKs in Tumor Cells 113
5.3	Therapy of Tumors with Dysregulated Growth Factors and their Receptors 115
5.3.1	Targeting Growth Factors 115
5.3.2	Targeting EGF Receptors by Antibodies 116
5.3.3	Targeting EGF Receptors by Kinase Inhibitors 117
5.4	Outlook 117
	References 117
<b>6</b>	<b>The Philadelphia Chromosome and BCR-ABL1 119</b>
6.1	Analysis of Chromosomes 120
6.2	Aberrant Chromosomes in Tumor Cells 121
6.3	The Philadelphia Chromosome 122
6.3.1	Molecular Diagnosis of the <i>BCR-ABL1</i> Fusion Gene 125
6.4	The BCR-ABL1 Kinase Protein 125
6.4.1	Structural Aspects of BCR-ABL1 Kinase 126
6.4.2	Substrates and Effects of BCR-ABL1 Kinase 128
6.4.3	The BCR-ABL1 Kinase Inhibitor Imatinib 129
6.4.4	Imatinib in Treatment of Tumors Other than CML 130
6.4.5	Mechanism of Imatinib Action 130
6.4.6	Resistance against Imatinib 130
6.4.7	BCR-ABL1 Kinase Inhibitors of the Second and the Third Generation 131
6.4.8	Allosteric Inhibitors of BCR-ABL1 132
6.5	Outlook 133
	References 133
<b>7</b>	<b>MAPK Signaling 135</b>
7.1	The <i>RAS</i> Gene 136
7.2	The Ras Protein 136
7.2.1	The Ras Protein as a Molecular Switch 138
7.2.2	The GTPase Reaction in Wild-Type and Mutant Ras Proteins 139
7.3	Neurofibromin: The Second RasGAP 143
7.4	Downstream Signaling of Ras 144
7.4.1	The BRAf Protein 145
7.4.2	The <i>BRAF</i> Gene 147
7.4.3	The MAPK Signaling Pathway 147
7.4.4	Mutations in Genes of the MAPK Pathway 148
7.5	Therapy of Tumors with Constitutively Active MAPK Pathway 149
7.5.1	Ras as a Therapeutic Target 150
7.5.1.1	Inhibiting Posttranslational Modification and Membrane Anchoring of Ras 150

7.5.1.2	Direct Targeting Mutant Ras	152
7.5.1.3	Preventing Ras/Raf Interaction	152
7.5.2	BRaf Inhibitors	152
7.5.2.1	Consequences of BRaf Inhibition by Vemurafenib	154
7.5.2.2	Resistance against BRaf Inhibitors Based on BRaf Dependent Mechanisms	154
7.5.2.3	Resistance against BRaf Inhibitors Based on BRaf Independent Mechanisms	155
7.5.2.4	Treatment of Vemurafenib-Resistant Tumors	155
7.6	Outlook	156
	References	156
<b>8</b>	<b>PI3K-AKT-mTOR Signaling</b>	<b>159</b>
8.1	Discovery of the PI3K-AKT-mTOR Pathway	160
8.2	Phosphatidylinositol-3-Kinase (PI3K)	161
8.3	Inositol Trisphosphate, Diacylglycerol, and Protein Kinase C (PKC)	163
8.3.1	Protein Kinase C (PKC)	163
8.3.2	Activation and Functions of PKC	165
8.4	AKT (Protein Kinase B)	165
8.5	mTOR	168
8.5.1	mTORC1: Inputs	170
8.5.2	mTORC2: Inputs	171
8.5.3	mTORC1: Outputs	171
8.5.4	mTORC2: Outputs	172
8.5.5	Feedback Controls	172
8.6	PTEN	172
8.7	Activation of the PI3K/AKT/mTOR Pathway in Cancer	173
8.7.1	Sporadic Carcinomas	173
8.7.2	Hamartoma Syndromes	174
8.8	PKC in Cancer	175
8.9	Therapy	176
8.10	Outlook	178
	References	180
<b>9</b>	<b>Hypoxia-Inducible Factor (HIF)</b>	<b>183</b>
9.1	Responses of HIF to Hypoxia and Oncogenic Pathways	184
9.2	HIF Functional Domains	185
9.3	Regulation of HIF	186
9.3.1	Regulation of HIF under Normoxic Conditions	186
9.3.2	Regulation of HIF under Hypoxic Conditions	189
9.3.3	Oxygen-Independent Regulation of HIF	189
9.3.4	Context-Dependence of HIF Regulation	190
9.4	Regulation of HIF in Malignant Disease	191
9.4.1	Expression of HIF in Human Tumors	191

9.4.2	von Hippel–Lindau Disease	191
9.5	HIF Targets in Cancer	192
9.5.1	Target Genes of HIF1 $\alpha$ and HIF2 $\alpha$	192
9.5.2	HIF Target Genes Affecting Tumor Growth	193
9.5.3	HIF Target Genes Affecting Metabolism	195
9.5.3.1	Glucose Uptake and Metabolism	195
9.5.3.2	HIF1 $\alpha$ and the Warburg Effect	197
9.5.3.3	The Warburg Paradox	197
9.6	TCA Cycle Intermediates and Tumor Syndromes	200
9.7	Drugs Targeting HIFs	200
9.8	Outlook	202
	References	203
10	<b>NF-<math>\kappa</math>B Pathways</b>	205
10.1	NF- $\kappa$ B Signaling in Inflammation, Growth Control, and Cancer	206
10.2	The Core of NF- $\kappa$ B Signaling	207
10.3	Family of I $\kappa$ B Proteins	209
10.4	Canonical NF- $\kappa$ B Signaling from TNF Receptor 1	210
10.5	B-Cell Receptor Signaling	213
10.6	Other Receptors Activating the Canonical Pathway	214
10.7	Alternative NF- $\kappa$ B Pathway	214
10.8	Terminating the NF- $\kappa$ B Response	215
10.9	Ubiquitinylation in NF- $\kappa$ B Signaling	217
10.10	Transcriptional Regulation	219
10.11	Physiological Role of NF- $\kappa$ B Transcription Factors	221
10.12	Mutational Activation of NF- $\kappa$ B Pathways in Malignant Disease	222
10.12.1	B-Cell Lymphomas	222
10.12.2	Multiple Myeloma	223
10.12.3	Activation of NF- $\kappa$ B Pathways by Polycomb-Mediated Loss of microRNA-31 in Adult T-Cell Leukemia/Lymphoma	225
10.12.4	Carcinomas	227
10.13	Cross Talk between Mutant KRas and NF- $\kappa$ B	227
10.14	Inflammation, NF- $\kappa$ B, and Cancer	228
10.15	Activation of Osteoclasts in Multiple Myeloma and Breast Cancer Metastases	230
10.16	Targeting NF- $\kappa$ B Pathways	232
10.16.1	B-Cell Malignancies	232
10.16.2	Carcinomas	233
10.16.3	Anti-Inflammatory Drugs	233
10.17	Outlook	233
	References	234

<b>11</b>	<b>Wnt Signaling</b>	<b>237</b>
11.1	The History of Wnt	238
11.2	The Canonical Wnt Pathway	238
11.2.1	The Nonactivated Wnt Pathway	239
11.2.2	The Physiologically Activated Wnt Pathway	241
11.2.3	The Nonphysiologically Activated Wnt Pathway in the Absence of the Wnt Signal	242
11.3	The Wnt Network	243
11.4	Proteins of the Wnt Pathway with Diverse Functions	243
11.4.1	APC (Adenomatous Polyposis Coli Protein)	243
11.4.2	$\beta$ -Catenin	245
11.4.3	Axin	245
11.5	The Wnt Targetome	246
11.5.1	The Three Levels of the Wnt Targetome	247
11.5.2	Biological Effects of Wnt Target Genes	248
11.6	The Wnt Pathway as Therapeutic Target	250
11.6.1	Strategies to Identify Anti-Wnt Drugs	250
11.6.2	Molecules Interfering with the Wnt Pathway	253
11.7	Outlook	254
	References	255
<b>12</b>	<b>Notch Signaling</b>	<b>257</b>
12.1	Introduction	258
12.2	Determination of Cell Fate Decisions	258
12.3	Notch Proteins and Notch Ligands	259
12.4	Notch Signaling	261
12.4.1	The Notch Signaling Pathway	261
12.4.2	Regulation of Notch Signaling by Posttranslational Modification	264
12.4.2.1	Ubiquitinylation	264
12.4.2.2	Glycosylation of Notch	265
12.5	Notch Signaling in Malignant Disease	266
12.5.1	Acute T-Cell Leukemia (T-ALL)	266
12.5.2	Chronic Lymphocytic Leukemia	268
12.5.3	Chronic Myelomonocytic Leukemia (CMML)	269
12.5.4	Breast Cancer	269
12.5.5	Cholangiocellular Carcinoma (CCC)	270
12.5.6	Squamous Cell Carcinomas (SCCs)	271
12.5.7	Small-Cell Lung Cancer (SCLC)	272
12.5.8	Angiogenesis	272
12.6	Drugs Targeting the Notch Pathway	273
12.7	Outlook	275
	References	275

<b>13</b>	<b>Hedgehog Signaling</b>	<b>277</b>
13.1	Overview of Hedgehog Signaling	278
13.2	Hedgehog Ligands	279
13.3	The Primary Cilium	280
13.4	Patched (Ptch) and Smoothened (Smo)	283
13.5	Gli Transcription Factors	283
13.6	Signaling in the Absence of Hedgehog	284
13.7	Signaling after Binding of Hedgehog to Patched	284
13.8	Activation of the Canonical Hedgehog Pathway in Basal Cell Carcinoma and Medulloblastoma	285
13.9	Noncanonical Activation of Hedgehog-Responsive Genes	288
13.9.1	KRas	288
13.9.2	Atypical Protein Kinase-Lambda/Iota (aPKC $\iota$ )	288
13.9.3	PI3-Kinase-AKT (PI3K-AKT)	289
13.9.4	mTOR	290
13.10	Paracrine Activation of Hedgehog Signaling	291
13.11	Pharmacological Inhibition of the Hedgehog Pathway	292
13.11.1	Inhibition of Hh Binding to Ptch	293
13.11.2	Inhibitors of Smoothened	293
13.11.3	Inhibition of Cilial Trafficking	294
13.11.4	Inhibition of Gli	294
13.11.5	Resistance against Direct Inhibitors of Smoothened	295
13.12	Outlook	296
	References	296
<b>14</b>	<b>TGF<math>\beta</math> Signaling</b>	<b>299</b>
14.1	The TGF $\beta$ Superfamily	300
14.2	Structure and Processing of TGF $\beta$ Superfamily Members	301
14.3	The TGF $\beta$ Signaling Pathway	302
14.4	Transcriptional Regulation by TGF $\beta$ Superfamily Members	305
14.5	Regulation of Stem Cells by TGF $\beta$ Superfamily Members	307
14.6	TGF $\beta$ Superfamily Members as Tumor Suppressors in Human Cancer	309
14.7	Active role of TGF $\beta$ in Tumor Progression	310
14.8	Drugs Interfering with TGF $\beta$ Signaling	312
14.9	TGF $\beta$ Superfamily Members in Tumor Cachexia	313
14.10	Outlook	315
	Nomenclature	316
	References	317
	<b>Index</b>	<b>319</b>