

Contents

Preface XXVII

1	Basics of Cell Signaling	1
1.1	Cell Signaling: Why, When, and Where?	1
1.2	Intercellular Signaling	3
1.2.1	Tools for Intercellular Signaling	3
1.2.2	Steps of Intercellular Signaling	5
1.2.2.1	Formation of a Signal in the Signal-Producing Cell as a Result of an External Trigger	5
1.2.2.2	Transport of the Signal to the Target Cell	6
1.2.2.3	Registration of the Signal in the Target Cell	6
1.2.3	Regulation of Intercellular Signaling	7
1.3	Hormones in Intercellular Signaling	8
1.3.1	The Chemical Nature of Hormones	8
1.3.2	Hormone Analogs: Agonists and Antagonists	11
1.3.2.1	Antagonists	11
1.3.2.2	Agonists	12
1.3.3	Endocrine, Paracrine, and Autocrine Signaling	13
1.3.3.1	Endocrine Signaling	14
1.3.3.2	Paracrine Signaling	15
1.3.3.3	Autocrine Signaling	15
1.3.4	Direct Protein Modification by Signaling Molecules	15
1.4	Intracellular Signaling: Basics	15
1.4.1	Reception of External Signals	16
1.4.2	Activation and Deactivation of Signaling Proteins	16
1.4.3	Processing of Multiple Signals	18
1.4.4	Variability of Signaling Proteins	18
1.5	Molecular Tools for Intracellular Signaling	18
1.5.1	Receptors	19
1.5.1.1	Receptors Receive External Signals and Trigger Intracellular Signaling	19
1.5.1.2	Membrane-Bound Receptors	20
1.5.1.3	Intracellular Receptors	21

1.5.1.4	The Interaction Between Hormone and Receptor	21
1.5.1.5	Regulation of Receptor Activity	22
1.5.2	Signaling Enzymes	23
1.5.3	Scaffolding Proteins	24
1.5.4	Diffusible Intracellular Messengers: Second Messengers	25
2	Structural Properties, Regulation and Posttranslational Modification of Signaling Proteins	27
2.1	Modular Structure of Signaling Proteins	27
2.1.1.1	Catalytic Domains	28
2.1.1.2	Targeting and Interaction Domains	28
2.1.1.3	Regulatory Domains	28
2.1.1.4	Unstructured, Flexible Sections	30
2.1.1.5	Multivalency	30
2.1.1.6	Differential Use of Modules	31
2.1.1.7	Multiple Inputs, Regulatory Influences, and Outputs	31
2.1.1.8	Subtypes of Signaling Modules	31
2.2	Modular Signaling Complexes	31
2.2.1.1	Specificity	33
2.2.1.2	Signal-Directed Assembly	33
2.2.1.3	Variability	33
2.2.1.4	Regulation	33
2.3	Regulation of Signaling Enzymes by Effector Binding	34
2.3.1.1	<i>Allostery</i> in Signaling Enzymes	34
2.3.1.2	Low-Molecular-Weight Effectors	35
2.3.1.3	Inhibitor Proteins	35
2.3.1.4	Activator Proteins	36
2.3.1.5	Metal Ions	36
2.4	Posttranslational Modifications (PTMs) in Cellular Signaling	36
2.4.1	Chemical Nature of PTMs	37
2.4.1.1	Allosteric and Conformational Functions of PTMs	38
2.4.1.2	Recognition of PTMs by Interaction Domains	38
2.4.1.3	Dynamic Nature of PTMs	38
2.4.1.4	Examples of Regulatory PTMs	38
2.4.2	Recognition of Protein Modifications by Modification-Specific Interaction Domains	41
2.4.3	Multisite Protein Modification	42
2.4.3.1	PTM Patterns are Used as a “Bar Code”	43
2.4.3.2	Multiple Modifications Often Show Combinatorial Characteristics	43
2.4.4	Binding Properties of Regulatory Interaction Domains	43
2.4.4.1	Versatility and Variability of Interaction Domains	46
2.4.5	How Interaction Domains Read PTM Patterns	47
2.4.5.1	Inducible Interactions	47
2.4.5.2	Cooperative Interactions and Multisite PTMs	47
2.4.5.3	Sequential PTM-Dependent Interactions and Cross-Regulation	47

2.4.5.4	Mutually Exclusive PTMs and Interactions	48
2.4.5.5	Antagonistic Action of PTMs	49
2.4.5.6	Regulation of Intramolecular Interactions by PTMs	49
2.4.5.7	Convergent Recognition of a PTM	50
2.5	Regulation by Protein Phosphorylation	51
2.5.1	General Aspects of Protein Phosphorylation	51
2.5.1.1	Properties and Interactions of Phosphorylated Proteins	52
2.5.2	Allosteric Functions of Protein Phosphorylation	53
2.5.3	Organization of Signaling Pathways by Protein Phosphorylation	54
2.5.3.1	Tyr-Phosphorylation	54
2.5.3.2	Ser/Thr Phosphorylation	54
2.6	Regulation by Protein Lysine Acetylation	55
2.6.1	General Aspects of Protein Lysine Acetylation	55
2.6.2	Enzymes of Protein Lysine Acetylation	56
2.6.2.1	HATs	56
2.6.2.2	HDACs	56
2.6.2.3	Cleavage Mechanism	57
2.6.3	Regulatory Functions of Lysine Acetylation	57
2.7	Regulation by Protein Methylation	58
2.7.1	Protein Lysine Methylation	58
2.7.1.1	Lysine Methyl Transferases	59
2.7.1.2	Lysine Demethylases, KDMs	59
2.7.1.3	Interaction Domains for Methylated Lysine	61
2.7.2	Protein Arginine Methylation	61
2.7.2.1	Arginine Demethylation/Citrullination	61
2.7.2.2	Interaction Domains	62
2.8	Ubiquitin Modification of Proteins	62
2.8.1	Pathways of Protein Degradation	63
2.8.1.1	Lysosomal Pathway	64
2.8.1.2	Autophagosomal Pathway	64
2.8.1.3	Proteasomal Pathway	64
2.8.2	Basics of Ubiquitin Modification	65
2.8.2.1	The Ub-Conjugation Reactions: E1, E2, and E3 Enzymes	66
2.8.2.2	E1: Activation of Ubiquitin	68
2.8.2.3	E2: Transacylation to the Ubiquitin-Conjugating Enzyme E2	68
2.8.2.4	E3: Ubiquitin Transfer to the Target	68
2.8.3	Structure and Regulation of Ub-Protein Ligases	69
2.8.3.1	Hect Domain E3 Enzymes	69
2.8.3.2	RING Domain E3 Enzymes	71
2.8.3.3	Structure and Regulation of Cullin-RING Ligases	73
2.8.3.4	Substrate Recognition by Cullin-RING Ligases	74
2.8.3.5	N-End Rule	74
2.8.3.6	Examples of Cullin-RINGE3 Ligases	75
2.8.3.7	SCF Complex	75
2.8.3.8	Anaphase-Promoting Complex (APC)	76

2.8.3.9	Cbl Proteins	77
2.8.4	Degradation in the Proteasome	78
2.8.4.1	The 20S Proteasome	78
2.8.4.2	The 19S Activator	80
2.8.5	Nonproteolytic Functions of Ubiquitin Conjugation	81
2.8.5.1	Deubiquitination	81
2.8.5.2	Multiplicity of Ub Conjugation	81
2.8.5.3	Ub-Binding Domains and Ub Receptors	84
2.8.5.4	Ub-Conjugation in Regulation of the NF κ B Pathway	85
2.8.6	Ubiquitin-Like Proteins: Sumo-Modification	88
2.9	Lipidation of Signaling Proteins	90
2.9.1	Myristoylation	91
2.9.2	Palmitoylation	92
2.9.2.1	Functions of Palmitoylation	93
2.9.3	Farnesylation and Geranylation	93
2.9.4	Dual Lipidation	95
2.9.5	Cholesterol Membrane Anchor	95
2.9.6	The Switch Function of Lipid Anchors	96
2.9.7	The Glycosyl-Phosphatidyl-Inositol (GPI) Anchor	98
	Questions	99
	References	100
3	Organization of Signaling	103
3.1	Scaffold Proteins	103
3.1.1	General Aspects of Scaffold Proteins	103
3.1.2	Scaffolds as Organizers of Signaling Circuits	105
3.1.2.1	Organization of Sequential Signaling and Signaling Circuits	106
3.1.2.2	Scaffolds Organize Signaling Complexes and are Targets of Regulation	107
3.1.2.3	Scaffolds Organize Feedback Loops	107
3.1.2.4	Scaffolds as Signaling Enzymes and Allosteric Regulators	108
3.2	Signal Processing in Signaling Paths and Signaling Networks	108
3.2.1	Specificity of Signaling	109
3.2.2	PTM-Induced Formation of Signaling Complexes	109
3.2.3	Signaling through Preassembled Multiprotein Complexes	110
3.2.4	Signaling in Dependence of Subcellular Localization: Spatial Organization	111
3.2.4.1	Spatial Control by Scaffolding	111
3.2.4.2	Spatial Control by Phosphorylation	112
3.2.4.3	Lipid Anchors	112
3.2.4.4	Clustering of Signaling Proteins on the Nanoscale	112
3.2.5	Temporal Control of Signaling	113
3.3	Architecture of Signaling Pathways	113
3.3.1	Linearity, Branching, Crosstalk, and Networks	114

3.3.1.1	Linearity	114
3.3.1.2	Branching	114
3.3.1.3	Crosstalk	114
3.3.1.4	Networks	115
3.3.2	Regulatory Circuits and Responses in Biological Networks	116
3.3.2.1	Circuits and Cascades	116
3.3.2.2	Feedback Loops	117
3.3.2.3	Negative Feedback	117
3.3.2.4	Positive Feedback	119
3.3.2.5	Bistability	120
3.3.2.6	Dynamic Behavior of Responses	121
3.3.3	Network Structures	121
3.3.3.1	Interaction Networks: Hubs	122
3.3.3.2	Layered Networks	124
3.3.3.3	Modularity	126
3.3.3.4	Redundancy and Robustness	126
	Questions	127
	References	127

4	The Regulation of Gene Expression	129
4.1	The Basic Steps of Gene Expression	129
4.1.1	Regulation of Transcription	129
4.1.1.1	Conversion of the pre-mRNA into the Mature mRNA	131
4.1.1.2	Regulation at the Level of mRNA and Translation	131
4.1.1.3	Nature of the Regulatory Signals	131
4.2	The Components of the Eukaryotic Transcription Machinery	131
4.2.1	The Basic Features of Eukaryotic Transcription	132
4.2.2	Elementary Steps of Eukaryotic Transcription	135
4.2.3	The Eukaryotic RNA Polymerases	135
4.2.4	The Core Promoter and Structure of the Transcription Start Site	137
4.2.5	General Transcription Factors and the Basal Transcription Apparatus	139
4.2.5.1	TFIID	139
4.2.5.2	TFIIF	141
4.2.6	The Mediator Complex	143
4.2.7	C-Terminal Domain (CTD) of RNA Polymerase II and the Onset of Transcription	146
4.3	The Principles of Transcription Regulation	149
4.3.1	Elements of Transcription Regulation	149
4.3.2	Regulation of Eukaryotic Transcription by Specific Transcription Factors	151
4.3.2.1	Activation and Repression of Transcription	152
4.3.3	Coregulators of Transcription	153
4.3.4	DNA-Binding of Specific Transcription Factors	153

4.3.4.1	DNA-Binding Domains	154
4.3.5	Structure of the Recognition Sequence and Quaternary Structure of DNA-Binding Proteins	155
4.3.5.1	Palindromic Arrangement	155
4.3.5.2	Direct Repeats of the Recognition Sequence	155
4.3.5.3	Identity of a RE	156
4.3.5.4	Homodimers and Heterodimers	156
4.3.6	Communication with the Transcription Apparatus: Transactivation Domains	157
4.3.7	Clustering of REs and the Enhanceosome	159
4.3.8	DNA Recognition and Selectivity of Transcription Activation	161
4.3.8.1	Sequence of the RE	161
4.3.8.2	Allostery in Transcription Factor–RE Interactions	162
4.3.8.3	Influence of Neighboring Sequences and Chromatin Surrounding	162
4.3.9	Repression of Transcription	163
4.4	The Control of Transcription Factors	165
4.4.1	Classification of Transcription Factors by their Function in Signal Transduction Networks	165
4.4.1.1	Constitutively Active Transcription Factors	166
4.4.1.2	Regulatory Transcription Factors	166
4.4.2	Mechanisms for the Control of the Activity of DNA-Binding Proteins	167
4.4.2.1	Changes in the Concentration of Regulatory DNA-Binding Proteins	169
4.4.2.2	Regulation by Binding of Effector Molecules	169
4.4.3	PTM of Transcription Regulators	170
4.4.3.1	Regulation by Phosphorylation	171
4.4.3.2	Regulation by Acetylation	175
4.5	Chromatin Structure and Transcription Regulation	175
4.5.1	Chromatin Architecture at Promoters	177
4.5.1.1	Histone Variants	180
4.5.1.2	Chromatin Remodeling	180
4.5.1.3	Chromatin Modification	182
4.5.2	Histone Acetylation	182
4.5.2.1	Histone Acetyltransferases	184
4.5.2.2	Histone Deacetylation	185
4.5.3	Histone Methylation	186
4.5.3.1	Enzymes of Histone Lysine Methylation	188
4.5.3.2	Enzymes of Histone Lysine Demethylation	189
4.5.3.3	Histone Arginine Methylation	189
4.5.4	Histone Phosphorylation	190
4.5.5	Histone Ubiquitination	192
4.5.6	Recognition of Histone Modifications by Protein Domains	192
4.5.7	Histone Modification Crosstalk	193

4.5.7.1	Crosstalk Mechanisms	194
4.5.7.2	Is There a Histone Modification “Code”?	196
4.5.8	Histone Modification and Epigenetics	197
4.5.9	DNA Methylation	197
4.5.9.1	DNA Methyltransferases	200
4.5.9.2	Coupling DNA Methylation to Gene Repression	200
4.5.9.3	Linking DNA Methylation and Histone Methylation	201
4.5.9.4	Biological Functions of DNA Methylation	202
4.5.10	Summary of the Regulatory Steps in Transcription	203
	Questions	205
	References	206

5 RNA Processing, Translational Regulation, and RNA Interference 209

5.1	Pre-mRNA Processing	209
5.1.1	Capping and Polyadenylation	210
5.1.1.1	Capping	210
5.1.1.2	Polyadenylation	210
5.1.2	Alternative Splicing	210
5.1.3	Regulation of Alternative Splicing	211
5.1.3.1	SR Proteins	213
5.1.3.2	hnRNPs	214
5.1.4	Chromatin Structure and Splicing	214
5.1.5	Coupling of pre-mRNA Processing, Transcription, and Translation	215
5.1.5.1	RNA Pol II Poised for Transcription	215
5.1.5.2	Formation of 5' Cap	215
5.1.5.3	Chromatin Modification and Start of Productive Elongation	215
5.1.5.4	Transcription and Nuclear Pores	216
5.1.5.5	Splicing During Transcription Elongation	216
5.1.5.6	RNA Pol II Termination	216
5.1.5.7	Linkage to Cytoplasmic Events	216
5.2	Regulation at the Level of Translation	217
5.2.1	Overview of Translation Initiation	217
5.2.2	The General Mechanisms of Translational Control	218
5.2.2.1	mRNA-Specific Control of Translation	219
5.2.2.2	Global Control of Translation	219
5.2.3	mRNA-Specific Regulation by 5'-Sequences: Control of Ferritin mRNA Translation by Iron	220
5.2.4	mRNA-Specific Translational Regulation by Protein Binding to 3'-UTRs	222
5.2.5	Global Translational Regulation of mRNAs by Targeting eIF-4E	222
5.2.5.1	4E-BP1 Phosphorylation	224
5.2.5.2	S6 Kinase Phosphorylation	226
5.2.6	Regulation of Translation via eIF-2	226
5.3	Regulation by RNA Silencing	229

5.3.1	Basics of RNA Silencing	230
5.3.2	The miRNAs	233
5.3.2.1	miRNA Biogenesis	233
5.3.2.2	Formation of miRISC	235
5.3.2.3	Posttranscriptional Repression and mRNA Decay	235
5.3.2.4	Regulation of miRNAs	238
5.3.2.5	Regulatory Functions of miRNAs	240
5.3.2.6	miRNAs and Cancer	243
5.3.3	siRNAs	243
5.3.3.1	Sources and Processing of siRNAs	243
5.3.3.2	Posttranscriptional Silencing by siRNAs	246
5.3.3.3	Functions and Applications of siRNAs	246
	Questions	247
	References	248
6	Signaling by Nuclear Receptors	251
6.1	Ligands of Nuclear Receptors (NRs)	252
6.2	Principles of Signaling by Nuclear Receptors (NRs)	254
6.3	Structure of Nuclear Receptors (NRs)	257
6.3.1	DNA-Binding Elements of NRs: HREs	258
6.3.2	The DNA-Binding Domain of NRs	260
6.3.3	Ligand-Binding Domain	261
6.3.3.1	Ligand Binding	262
6.3.3.2	Ligand Binding and AF-2 Function	263
6.3.3.3	Switch Function of Ligand Binding	264
6.3.3.4	Promiscuous Ligand Binding	265
6.3.4	Transactivation Functions of the NRs	265
6.3.5	Structure of an Intact NR Complex on DNA	266
6.3.6	Orphan Nuclear Receptors	268
6.4	Transcriptional Regulation by NRs	268
6.4.1	Coregulators in NR Function	269
6.4.2	NR Coactivators	271
6.4.2.1	SRC/p160 Family of Coactivators	271
6.4.2.2	TRAP Complex, Mediator	273
6.4.2.3	Variability of Coactivator Recruitment	273
6.4.3	Corepressors of NRs	274
6.5	Regulation of Signaling by Nuclear Receptors	274
6.5.1	Regulation at the Level of Ligand Concentration	275
6.5.2	Regulation by PTM	276
6.5.2.1	Regulation by Phosphorylation	276
6.5.3	Ubiquitination and Sumoylation of NRs	278
6.5.4	Composite DNA Elements, Interaction with Other Transcription Factors, and Long-Range Effects	278
6.5.4.1	Crosstalk with Other Transcription Factors	279
6.5.4.2	Long-Range Actions of NRs	279

6.5.5	Determinants of Cell- and Gene-Specificity of NR Action	280
6.6	Subcellular Localization of NRs	280
6.6.1	Nuclear and Cytoplasmic Pools	281
6.6.2	Other Subcellular Pools	281
6.6.3	Ligand-Dependent Translocation of Nuclear Receptors	281
6.6.4	Nuclear Translocation	283
6.7	Nongenomic Functions of NRs and their Ligands	284
6.7.1	Nuclear Receptor Functions Outside of the Nucleus	284
6.7.1.1	Cytoplasmic Functions	284
6.7.1.2	ER Actions at the Cell Membrane	285
6.7.1.3	NR Action at the Mitochondrion	288
6.7.2	Hormone Binding to Other Receptor Types	288
	Questions	289
	References	289
7	G Protein-Coupled Signal Transmission Pathways	291
7.1	Transmembrane Receptors: General Structure and Classification	291
7.1.1	Signaling via Transmembrane Receptors	291
7.1.2	Signaling via Ligand- or Voltage-Gated Ion Channels	292
7.2	Structural Principles of Transmembrane Receptors	294
7.2.1	The Extracellular Domain of Transmembrane Receptors	294
7.2.2	The Transmembrane Domain	296
7.2.2.1	Structure of Transmembrane Elements	296
7.2.3	The Intracellular Domain of Membrane Receptors	298
7.2.3.1	Recruitment of Downstream Signaling Proteins	298
7.2.3.2	Triggering of Enzyme Activity	299
7.2.4	Regulation of Receptor Activity	300
7.2.4.1	Receptor Phosphorylation and Receptor Recycling	300
7.2.4.2	Ubiquitination and Degradation	301
7.3	G Protein-Coupled Receptors	301
7.3.1	Classification of GPCRs	304
7.3.2	Structure of G Protein-Coupled Receptors	305
7.3.2.1	Overall Structure	307
7.3.2.2	Ligand Binding and Effector Activation	309
7.3.2.3	Binding of Activated GPCR to G Protein	310
7.3.2.4	Ligand-selective GPCR Signaling	311
7.3.3	Regulation of GPCRs	312
7.3.3.1	Phosphorylation of GPCRs	314
7.3.3.2	Desensitization and Downregulation of GPCRs	315
7.3.3.3	GPCR Phosphorylation by GRKs	316
7.3.3.4	Binding of Arrestin	317
7.3.3.5	Signal Switching	319
7.3.3.6	Coupling to other Signaling Pathways	319
7.3.4	Oligomerization of GPCRs	319

7.4	Regulatory GTPases	320
7.4.1	The GTPase Superfamily: General Functions	321
7.4.2	Switch Functions of GTPases and the GTPase Cycle	321
7.4.2.1	Modulation and Regulation of the Switch Function	323
7.4.3	Inhibition of GTPases by GTP Analogs	324
7.4.4	The G-Domain as a Common Structural Element of the GTPases	325
7.4.5	The GTPase Families	326
7.5	The Heterotrimeric G Proteins	327
7.5.1	Classification of the Heterotrimeric G Proteins	328
7.5.1.1	G_s Subfamily	331
7.5.1.2	G_i Subfamily	331
7.5.1.3	G_q Subfamily	332
7.5.1.4	G_{12} Subfamily	332
7.5.2	Toxins as Tools in the Characterization of Heterotrimeric G Proteins	332
7.5.3	The Functional Cycle of Heterotrimeric G Proteins	334
7.5.3.1	Inactive Ground State	334
7.5.3.2	Activation	334
7.5.3.3	Transmission of the Signal	336
7.5.3.4	Termination of the Signal and GTPase-Activating Proteins	336
7.5.3.5	Heterotrimeric G Proteins in Supramolecular Complexes	337
7.5.4	Structural and Mechanistic Aspects of the Switch Function of G Proteins	337
7.5.4.1	Coupling of the Activated Receptor to the G Protein	337
7.5.4.2	Structure of the G_α -subunit	337
7.5.4.3	Structure of the Heterotrimer	339
7.5.4.4	Conformational Changes Upon Activation by GTP	339
7.5.4.5	Mechanism of GTP Hydrolysis	340
7.5.4.6	Acceleration of GTP Hydrolysis by GTPase-Activating Proteins	342
7.5.5	Structure and Function of the $G_{\beta\gamma}$ -Complex	342
7.5.5.1	Structure of the $G_{\beta\gamma}$ -Complex	343
7.5.5.2	Specificity of $G\beta\gamma$ Signaling	343
7.5.5.3	Signaling by the $\beta\gamma$ -Complex	344
7.5.6	Membrane Association of the G Proteins	345
7.5.7	Regulators of G Proteins: Phosducin and RGS Proteins	346
7.5.7.1	Phosducin	347
7.5.7.2	RGS Proteins	347
7.5.7.3	Non-G Protein Signaling by RGS Proteins	349
7.6	Receptor-independent Functions of Heterotrimeric G Proteins	350
7.6.1	Novel G Protein Cycle	350
7.7	Effector Molecules of G Proteins	352
7.7.1	Adenylyl Cyclase and cAMP as “Second Messenger”	352
7.7.1.1	Structure of Adenylyl Cyclase	354
7.7.1.2	Regulation of Adenylyl Cyclase	355

7.7.2	Phospholipase C	357
7.7.2.1	Phospholipase C- β	360
7.7.2.2	Phospholipase C- γ	362
7.7.2.3	Phospholipases C- δ	362
7.7.2.4	Phospholipase C- ϵ	362
7.8	GPCR Signaling via Arrestin	363
	Questions	365
	References	366
8	Intracellular Messenger Substances: “Second Messengers”	369
8.1	General Properties of Intracellular Messenger Substances	369
8.2	Cyclic AMP	371
8.2.1	Formation and Degradation of cAMP	371
8.2.1.1	Formation by ACs	371
8.2.1.2	Phosphodiesterases and cAMP Breakdown	372
8.2.2	Targets of cAMP	372
8.2.3	Compartmentalization of cAMP Signaling	374
8.3	cGMP and Guanylyl Cyclases	375
8.3.1	Guanylyl Cyclases	375
8.3.1.1	Guanylyl Cyclase Receptors	376
8.3.1.2	Soluble Guanylyl Cyclases	377
8.3.2	Targets of cGMP	377
8.4	Metabolism of Inositol Phospholipids and Inositol Phosphates	378
8.4.1	Other Inositol Messengers	380
8.4.2	Activation of PLC and Inositol Phosphate Formation	381
8.5	Storage and Release of Ca ²⁺	383
8.5.1	Release of Ca ²⁺ from Ca ²⁺ Storage	384
8.5.1.1	The InsP ₃ Receptor	384
8.5.1.2	The Ryanodine Receptor	387
8.5.1.3	cADP-Ribose and NAADP	387
8.5.1.4	Ca ²⁺ Channels and Apoptosis	388
8.5.1.5	Tool Kit for Ca ²⁺ Release	389
8.5.2	Influx of Ca ²⁺ from the Extracellular Region	390
8.5.3	Removal and Storage of Ca ²⁺	390
8.5.4	Temporal and Spatial Changes in Ca ²⁺ Concentration	391
8.5.4.1	Calcium Oscillations	392
8.6	Functions of Phosphoinositides	392
8.6.1	The Messenger Function of PtdIns(3,4,5)P ₃	393
8.6.2	Functions of PtIns(4,5)P ₂ and Other Phosphoinositides	393
8.7	Ca ²⁺ as a Signal Molecule	394
8.7.1	The EF Hand: A Ca ²⁺ -Binding Module	396
8.7.2	Calmodulin as a Ca ²⁺ Sensor	398
8.7.3	Target Proteins of Ca ²⁺ /Calmodulin	399
8.7.4	Other Ca ²⁺ Sensors	399

8.8	Diacylglycerol as a Signal Molecule	401
8.9	Other Lipid Messengers: Ceramide, Sphingosine, and Lysophosphatidic Acid	401
8.9.1	Ceramide	402
8.9.2	Sphingosine	403
8.9.3	Lysophosphatidic Acid (LPA)	404
8.10	The NO Signaling Molecule	404
8.10.1	Reactivity of NO	405
8.10.2	Synthesis of NO	407
8.10.2.1	nNOS	408
8.10.2.2	eNOS	408
8.10.2.3	iNOS	409
8.10.3	Physiological Functions of Nitrosylation	409
8.10.4	Nitrosylation of Metal Centers	409
8.10.4.1	NO-Sensitive Guanylyl Cyclase	409
8.10.4.2	Nitrosylation of Hemoglobin	410
8.10.5	Regulatory Functions of Protein S-Nitrosylation	411
8.10.5.1	Selectivity of Protein S-Nitrosylation	411
8.10.5.2	Transnitrosylation	412
8.10.5.3	Denitrosylation	412
8.10.5.4	Target Proteins for S-Nitrosylation	413
8.10.6	Toxic Action of NO and Nitrosative Stress	413
	Questions	414
	References	415
9	Ser/Thr-Specific Protein Kinases and Protein Phosphatases	417
9.1	Classification, Structure, and Characteristics of Protein Kinases	417
9.2	Structure and Regulation of Protein Kinases	420
9.2.1	The Protein Kinase Reaction	421
9.2.2	Main Structural Elements of Protein Kinases	422
9.2.3	Substrate Binding and Recognition	425
9.2.4	Control of Protein Kinase Activity	427
9.2.5	Regulation of Protein Phosphorylation by Subcellular Localization and Specific Targeting Subunits	430
9.3	Protein Kinase A	431
9.3.1	Structure and Substrate Specificity of PKA	432
9.3.2	Regulation of PKA	435
9.3.3	A-Kinase Anchor Proteins (AKAPs)	436
9.3.3.1	AKAPs as Multivalent Scaffolds	436
9.4	The PI3 Kinase/Akt Pathway	439
9.4.1	PI3K	440
9.4.1.1	Classification and Properties of PI3K	440
9.4.1.2	Activation of PI3K	441
9.4.2	Akt Kinase (PKB)	442
9.4.2.1	Activation of Akt Kinase	443

9.4.2.2	Signaling by Akt Kinase	444
9.4.2.3	Phosphatase and Tensin Homolog PTEN Phosphatase	446
9.5	Protein Kinase C	447
9.5.1	Classification and Structure of PKC	447
9.5.2	The Protein Kinase C Family	447
9.5.2.1	Stimulation by Phorbol Esters	449
9.5.3	Activation of PKC	449
9.5.4	Regulation of Protein Kinase C	450
9.5.4.1	Regulation by Ca^{2+} and DAG	451
9.5.4.2	Regulation by Phosphorylation: PDK1	452
9.5.4.3	Protein Kinase C-Interacting Proteins and Regulation by Localization	453
9.5.5	Receptors for Protein Kinase C, RACK Proteins	453
9.5.6	Functions and Substrates of PKC	454
9.6	Ca^{2+} /Calmodulin-Dependent Protein Kinases, CaM Kinases	455
9.6.1	General Function of CaM Kinases	455
9.6.2	CaM Kinase II	456
9.6.2.1	Structure and Activation of CaMKII	457
9.6.2.2	Memory Function of CaMKII	460
9.7	Ser/Thr-Specific Protein Phosphatases	461
9.7.1	Classification and Structure of Ser/Thr Protein Phosphatases	462
9.7.2	Function and Regulation of Ser/Thr Protein Phosphatases	462
9.7.3	Protein Phosphatase I, PPI	464
9.7.4	Protein Phosphatase 2A, PP2A	465
9.7.5	Protein Phosphatase 2B, Calcineurin	467
	Questions	469
	References	470
10	Signal Transmission via Transmembrane Receptors with Tyrosine-Specific Protein Kinase Activity	473
10.1	Structure and Function of RTKs	474
10.1.1	General Structure and Classification	475
10.1.2	Ligand Binding and Receptor Dimerization	477
10.1.2.1	Receptor Heterodimerization	481
10.1.3	Structure and Activation of the TK Domain	481
10.1.3.1	Autoinhibition by the Activation Loop: The Insulin Receptor	483
10.1.3.2	Juxtamembrane Autoinhibition	484
10.1.3.3	Autoinhibition by C-Terminal Sequences	484
10.1.3.4	Allosteric Mechanism of Activation	485
10.1.4	RTK Activation and Downstream Signaling	485
10.1.4.1	Nucleation of Signaling Complexes	485
10.1.5	Recruitment of Effectors via Interaction Domains	490
10.1.5.1	SH2 Domains	491
10.1.5.2	P-Tyrosine-Binding (PTB) Domain	493
10.1.5.3	C2 Domains	493

10.2	Downstream Effector Proteins of RTKs	494
10.2.1	Adapter Proteins in RTK Signaling	494
10.2.1.1	Insulin Receptor Substrate (IRS)	495
10.2.1.2	Tyr-Phosphorylation: Effector Recruitment	495
10.2.1.3	Ser/Thr Phosphorylation: Signal Dampening	496
10.2.2	Adaptor Proteins: FRS, Grb2, Gab, Shc, LAT, and p130 Cas	497
10.2.2.1	Fibroblast Growth Factor Receptor Substrate (FRS)	497
10.2.2.2	Grb2	497
10.2.2.3	Gab	499
10.2.2.4	Shc	499
10.2.2.5	PDZ-Containing Adapter Proteins	500
10.2.2.6	LAT	500
10.2.2.7	p130Cas	500
10.2.3	Downstream Effectors of RTK Signaling	500
10.2.4	RTKs as Part of Signaling Networks	501
10.2.5	Attenuation and Feedback Regulation in RTK Signaling	504
10.2.5.1	Antagonistic Ligands, Heterodimerization	505
10.2.5.2	Inhibition by Inhibitor Proteins	505
10.2.6	Endocytosis and Trafficking of RTKs	506
10.2.6.1	Ubiquitination	506
10.2.7	RTK Dysfunction in Disease	506
10.3	Nonreceptor Tyrosine-Specific Protein Kinases, Non-RTKs	507
10.3.1	Structure and General Function of Non-RTKs	507
10.3.1.1	Functions of non-RTKs	508
10.3.2	Src Tyrosine Kinase	508
10.3.2.1	Structure of Inactive Src	509
10.3.2.2	Inactive State of Src	511
10.3.2.3	Activation of Src	511
10.3.3	Abl Tyrosine Kinase	513
10.3.3.1	Structure of Abl	513
10.3.3.2	Activation of Abl	515
10.3.3.3	Substrate Selection and Interaction Partners of Abl	515
10.3.3.4	Regulation of Abl	517
10.3.3.5	Cellular Functions of Abl	517
10.3.3.6	Oncogenic Activation of Abl	518
10.4	Protein Tyrosine Phosphatases	519
10.4.1	General Functions of PTPs	519
10.4.2	Classification, Structure, and Mechanism of PTPs	520
10.4.3	Catalytic Mechanism of PTPs	520
10.4.3.1	Receptor Protein Tyrosine Phosphatases (PTPRs)	521
10.4.3.2	Nonreceptor Protein Tyrosine Phosphatases (PTPNs)	523
10.4.3.3	Autoinhibition of PTPN Enzymes	523
10.4.4	Regulation of Cell Signaling by PTPs	525
10.4.4.1	Negative Regulation by PTPs, and Tumor Suppression	526
10.4.4.2	Positive Regulation by PTPs, and Oncogenic Functions	526

10.4.5	Regulation of PTP Activity	527
10.4.6	Oxidation of PTPs	528
10.4.7	Subcellular Localization of PTPs	532
	Questions	532
	References	533
11	Signal Transmission via Ras Proteins	535
11.1	The Ras Superfamily of Monomeric GTPases	535
11.1.1	Crosstalk Among Ras Superfamily Members	538
11.2	GTPase-Activating Proteins (GAPs) of the Monomeric GTPases	539
11.3	Guanine Nucleotide Exchange Factors (GEFs) of the Monomeric GTPases	541
11.3.1	Catalytic Domains	541
11.3.1.1	Mechanism of Nucleotide Exchange	542
11.3.1.2	Multivalency of GEFs	542
11.3.1.3	GEFs Can Activate Two Different GTPases	543
11.3.1.4	GEFs as Effectors of GTPases: Linkage of and Crosstalk between GTPases	543
11.4	Guanine Nucleotide Dissociation Inhibitors (GDIs)	544
11.5	The Ras Family of Monomeric GTPases	545
11.5.1	General Properties of the Ras Protein	545
11.5.2	Structure of the GTP- and GDP-Bound Forms of Ras Protein	547
11.5.3	GTP Hydrolysis Mechanism and Stimulation by GAPs	548
11.5.4	Structure and Biochemical Properties of Transforming Mutants of Ras Protein	550
11.5.5	Membrane Localization of Ras Protein	551
11.5.5.1	Ras Nanoclusters	551
11.5.6	GAPs in Ras Signal Transduction	552
11.5.7	Guanine Nucleotide Exchange Factors (GEFs) in Ras Signal Transduction	553
11.5.7.1	Structure and Activation	553
11.5.7.2	Regulation	554
11.6	Raf Kinase as an Effector of Signal Transduction by Ras Proteins	555
11.6.1	Structure of Raf kinase	557
11.6.2	Mechanism of Activation and Regulation of Raf Kinase	557
11.6.2.1	Formation of Homodimers and Heterodimers	559
11.6.2.2	Negative Feedback by Inhibitory Phosphorylations	560
11.6.3	Oncogenic Activation of Raf	561
11.7	Further Ras Family Members: R-Ras, Ral, and Rap	561
11.8	Reception and Transmission of Multiple Signals by Ras Protein	562
11.8.1	Multiple Input Signals of Ras Protein	562
11.8.2	Multiple Effector Molecules of Ras Proteins	564
11.8.3	The Ras Signaling Network	566
11.9	The Further Branches of the Ras Superfamily	568
11.9.1	The Rho/Rac Family	568

11.9.2	The Rab Family	569
11.9.3	The Ran Family	570
11.9.4	The Arf Family	570
	Questions	570
	References	571
12	Intracellular Signal Transduction: The MAP Kinase Pathways	573
12.1	Organization and Components of MAPK Pathways	575
12.1.1	MAPKs	577
12.1.2	MAPK Kinases (MAP2Ks, MEKs)	577
12.1.3	MEK Kinases (MAPKK Kinases, MAP3Ks)	579
12.2	Regulation of MAPK Pathways by Protein Phosphatases and Inhibitor Proteins	579
12.2.1	Feedback Loops in MAPK Regulation	580
12.2.2	Regulation by MAPK Phosphatases	581
12.2.3	MAPK Regulation by Inhibitory Proteins	583
12.3	Scaffolding in MAPK Signaling	583
12.4	The Major MAPK Pathways of Mammals	586
12.4.1	The ERK Pathway	586
12.4.1.1	Input Signals	586
12.4.1.2	Substrates of ERKs	587
12.4.2	The JNK and p38 MAPK Pathways	588
12.4.2.1	Input Signals and Signal Entry Points of the JNK and p38 Pathways	589
12.4.2.2	Substrates of the JNK and p38 Pathways	590
12.4.2.3	The JNK Module	591
12.4.2.4	The p38 Module	591
	Questions	592
	References	592
13	Membrane Receptors with Associated Tyrosine Kinase Activity	593
13.1	Cytokines and Cytokine Receptors	593
13.1.1	Cytokines	594
13.1.1.1	Cytokine Structure	595
13.1.1.2	General Functions of Cytokines	595
13.1.2	Structure and Activation of Cytokine Receptors	596
13.1.2.1	Classification and General Features	596
13.1.2.2	Structural Domains	597
13.1.2.3	Oligomeric Structure	598
13.1.2.4	Cytokine Binding and Activation	599
13.1.2.5	Gp130 Receptors	601
13.1.2.6	Shared γ -Chain Receptors	603
13.1.2.7	Shared β -Chain Receptors	603
13.1.3	Activation of Cytoplasmic Tyrosine Kinases	604
13.2	The Jak-STAT Pathway	608

13.2.1	The Janus Kinases	609
13.2.1.1	Kinase Regulation	609
13.2.1.2	Coupling to Other Receptor Types	610
13.2.1.3	Nuclear Functions of Jak	610
13.2.2	The Stat Proteins	611
13.2.2.1	Structure of Stats	612
13.2.2.2	Activation of Stats	612
13.2.2.3	Signaling Function of STATs	614
13.2.2.4	Signaling by Unphosphorylated STATs	615
13.2.2.5	Acetylation of STATs	615
13.2.3	Regulation of Cytokine Receptor Signaling	615
13.2.3.1	Protein Tyrosine Phosphatases	617
13.2.3.2	SOCS Proteins	617
13.2.3.3	PIAS (Protein Inhibitors of Activated Stats)	617
13.3	T- and B-Cell Receptors	618
13.3.1	Immunoreceptor Structure	618
13.3.1.1	T-Cell Receptor Structure	618
13.3.1.2	B-Cell Receptor Structure	619
13.3.2	Activation and Signaling of the T-Cell Antigen Receptors	621
13.3.2.1	Initiation of Signaling	621
13.3.2.2	Zap70	621
13.3.2.3	LAT (Linker for Activation of T Lymphocytes)	623
13.4	Signal Transduction via Integrins	623
13.4.1.1	Talin and Kindlin as Key Activators	625
13.4.1.2	Downstream Signaling	626
13.4.1.3	Focal Adhesion Kinase (FAK)	627
	Questions	628
	References	629
14	Other Transmembrane Receptor Classes: Signaling by TGF-β Receptors, TNF Receptors, Toll Receptors, and Notch	631
14.1	Receptors with Intrinsic Ser/Thr Kinase Activity: The TGF- β Receptor and Smad Protein Signaling	631
14.1.1	The Family of TGF- β Cytokines	633
14.1.2	TGF- β Receptor	634
14.1.2.1	TGF- β Receptor Structure	635
14.1.2.2	TGF- β Receptor Activation	635
14.1.2.3	Non-Smad Signaling Pathways	636
14.1.3	Smad Proteins	636
14.1.3.1	Smad Activation	638
14.1.3.2	DNA Binding and Transcriptional Regulation by Smads	640
14.1.4	Regulation of TGF- β and Smad Signaling	640
14.1.4.1	Inhibition by I-Smads	641
14.1.4.2	Ubiquitination and Sumoylation	641
14.1.4.3	Phosphorylation	641

14.1.4.4	Activation of Smad Expression	641
14.1.4.5	Growth Regulatory Effects of TGF- β Signaling	642
14.2	Receptor Regulation by Intramembrane Proteolysis: The Notch Receptor	642
14.2.1	Notch: General Function, Structure, and Ligands	643
14.2.1.1	Regulated Intramembrane Proteolysis	643
14.2.1.2	Domain Organization of Notch	644
14.2.1.3	Notch Ligands	644
14.2.2	Processing and Activation of Notch	644
14.2.2.1	Transcription Activation	648
14.3	Tumor Necrosis Factor Receptor (TNFR) Superfamily	648
14.3.1	Biological Functions of TNFR Signaling	650
14.3.2	TNFR Structure	650
14.3.3	TNF Cytokines	651
14.3.4	Receptor Activation and Downstream Signaling	652
14.3.4.1	Downstream Signaling	652
14.3.4.2	Recruitment of Adapter Proteins and Activation of NF κ B Pathways	652
14.4	Toll-Like Receptor Signaling	653
14.4.1	TLR Structure	654
14.4.1.1	Ligand Binding and Activation	655
14.4.1.2	TLR Adaptors and Further Signaling	656
14.4.1.3	Adapter-Mediated Downstream Signaling	657
	Questions	658
	References	659
15	Cell-Cycle Control by External Signaling Pathways	661
15.1	Principles of Cell-Cycle Control	661
15.1.1	Intrinsic Control Mechanisms	663
15.1.2	External Cell Cycle Control	664
15.1.2.1	Mitogenic Signals	664
15.1.2.2	Antimitogenic Signals during Cell–Cell Communication	665
15.1.3	Cell-Cycle Checkpoints	665
15.2	Key Elements of the Cell-Cycle Apparatus	666
15.2.1	Cyclin-Dependent Protein Kinases (CDKs)	666
15.2.1.1	CDKs Involved in Cell-Cycle Regulation	667
15.2.1.2	Other CDKs	667
15.2.2	Cyclins	667
15.2.2.1	Regulation of Cyclin Concentration	670
15.2.3	Inhibitors of CDKs: The CKIs	671
15.2.3.1	Regulation and Function of CKIs	672
15.2.3.2	The CIP/KIP Family	672
15.2.3.3	INK4 Proteins	674
15.2.4	Structural Basis of CDK Regulation	674
15.2.4.1	CDK–Cyclin Complexes	674

15.2.4.2	Phosphorylation of CDKs	676
15.2.4.3	Structural Basis of Inhibition by p27 ^{KIP1}	677
15.2.5	Multiple Regulation of CDKs	678
15.2.6	Substrates of CDKs	679
15.2.6.1	Substrates in G ₁ /S Phase	679
15.2.6.2	Substrates in G ₂ /M Phase	680
15.3	Regulation of the Cell Cycle by Proteolysis	681
15.3.1	Proteolysis Mediated by the SCF Complex	682
15.3.2	Proteolysis Mediated by the APC/Cyclosome	684
15.4	G ₁ Progression and S Phase Entry	684
15.4.1	CDK4/6 and the D-Type Cyclins	685
15.4.1.1	Regulation of CDK4–cyclin D1	685
15.4.2	Function of CDK2–Cyclin E in S Phase Entry	687
15.4.3	Function of the Retinoblastoma protein (Rb) in the Cell Cycle	687
15.4.3.1	Domain Structure of Rb	689
15.4.3.2	Control of Rb by Phosphorylation	690
15.4.4	The E2F Transcription Factors and their Control by Rb	691
15.4.4.1	Control of E2Fs by Rb	692
15.4.5	Summary of G ₁ Progression	694
15.4.6	Mitogenic Signals Regulating G ₁ Entry and Progression	694
15.4.6.1	Transcriptional Control of Cyclin D1	695
15.4.6.2	Control of Cyclin D1 Translation and Stability	696
15.4.7	Negative Regulation of the G ₁ /S Transition	697
15.4.8	Integration of Mitogenic Signals for Control of Cell Proliferation, Cell Growth, and Survival	697
15.5	Transit Through S Phase and M Phase	699
15.5.1	DNA Replication During S Phase	699
15.5.2	G ₂ /M Transition and Progression Through M Phase	700
15.5.2.1	CDK1 Control at G ₂ /M	700
15.5.2.2	Progression Through M Phase	702
15.6	DNA Damage and DNA Replication Checkpoints	702
15.6.1	Components and Organization of DNA Damage Checkpoints	703
15.6.1.1	Recognition of DNA Damage or Sensing of Replication Stress	707
15.6.1.2	Functions of ATM	708
15.6.1.3	Functions of ATR	709
15.6.1.4	Chk1, Chk2, and Downregulation of CDC25 Phosphatase	709
15.6.2	The Mammalian G ₁ DNA Damage Checkpoint	710
15.6.3	The G ₂ /M Checkpoint	712
	Questions	712
	References	713
16	Malfunction of Signaling Pathways and Tumorigenesis: Oncogenes and Tumor Suppressor Genes	715
16.1	Basic Characteristics of Tumor Cells	715
16.2	Mutations in Cancer Cells	715

16.2.1	Genetic Changes in Cancer Cells	716
16.2.1.1	Small-Scale Changes	717
16.2.1.2	Large-Scale Changes and Genetic Instability	717
16.2.2	Epigenetic Changes in Tumor Cells	717
16.2.2.1	Altered DNA Methylation	718
16.2.2.2	Altered Histone Modifications in Cancer	720
16.2.2.3	Micro RNAs and Cancer	720
16.2.3	Cancer Genes: Drivers and Passengers	721
16.2.3.1	Oncogenes Versus Tumor Suppressor Genes	722
16.2.4	Carcinogenesis as an Evolutionary Process	722
16.3	Common Physiologic Changes in Tumor Cells: The Hallmarks of Cancer	725
16.3.1	Self-Sufficiency in Growth Signals	727
16.3.2	Insensitivity to Antigrowth Signals	728
16.3.3	Evasion of Programmed Cell Death (Apoptosis)	729
16.4	Signaling Proteins Mutated in Cancer: Oncogenes	729
16.4.1	Mechanisms of Oncogene Activation	730
16.4.1.1	Oncogenic Activation by Structural Changes	730
16.4.1.2	Oncogenic Fusion Proteins	731
16.4.1.3	Activation by Protein Concentration Increase	732
16.4.2	Examples of the Functions of Oncogenes	733
16.4.2.1	Oncogenic Receptor Tyrosine Kinases: The ErbB2/neu Receptor	734
16.4.2.2	Oncogenic Nonreceptor Tyrosine Kinases	735
16.4.2.3	Oncogenic Activation of Ras Signaling Pathways	737
16.4.2.4	Oncogenic Activation of Cyclins	737
16.4.2.5	Oncogenic Transcription Factors: Myc	737
16.5	Tumor Suppressor Genes: General Functions	741
16.6	Tumor Suppressors: Rb and ARF Proteins	743
16.6.1	Rb in Cancer	743
16.6.1.1	Rb and Apoptosis	744
16.6.2	The p16 ^{INK4a} Gene Locus and ARF	746
16.7	Tumor Suppressor Protein p53	747
16.7.1	Overview of p53 Function	749
16.7.1.1	Cousins of p53	751
16.7.2	Structure and Biochemical Properties of the p53 Protein	751
16.7.3	Structure of p53	752
16.7.4	PTMs of p53	753
16.7.4.1	Phosphorylation	753
16.7.4.2	Acetylation	755
16.7.4.3	Methylation	755
16.7.4.4	Ubiquitination	756
16.7.4.5	Neddylation, Sumoylation	756
16.7.5	Control of p53 by Mdm2	756
16.7.5.1	Mdm2 is an Oncogene	757
16.7.5.2	Negative Feedback Between p53 and Mdm2	757

16.7.5.3	Other Controls of Mdm2 Function	759
16.7.5.4	p53-Independent Functions of Mdm2	759
16.7.6	Genes Regulated by p53	760
16.7.6.1	Selection of Target Genes	760
16.7.7	Pathways Involved in the Activation of p53	762
16.7.7.1	Activation of p53 by DNA Damage	762
16.7.7.2	Activation of p53 by Oncogenic Stress	762
16.7.7.3	Activation of p53 by Nongenotoxic Stress	763
16.7.8	Classification of p53 Target Genes	763
16.7.8.1	p53 Targets Activated in Unstressed Cells and Under Low Intrinsic Stress	764
16.7.8.2	p53 Targets Activated by Moderate Stresses	764
16.7.8.3	p53 Targets Activated by Sustained or Severe Stress	766
16.7.8.4	p53-Mediated Repression	767
16.7.9	Metabolic Regulation by p53	767
16.7.10	p53-Mediated Induction of miRNA	768
16.7.11	Summary of Tumor Suppression by p53	768
16.8	Wnt/β-Catenin Signaling and the Tumor Suppressor APC	770
16.8.1	APC	770
16.8.1.1	Downregulation of β-Catenin	772
16.8.1.2	Activation of β-Catenin	772
	Questions	773
	References	774
17	Apoptosis	777
17.1	Overview of Apoptotic Pathways	778
17.2	Caspases: Death by Proteolysis	779
17.2.1	Initiator and Effector Caspases	780
17.2.1.1	Initiator Caspases	781
17.2.1.2	Effector Caspases	781
17.2.2	Mechanism of Caspases	781
17.2.3	Caspase Activation and Regulation	783
17.2.3.1	Death Platforms	783
17.2.3.2	Activation of Initiator Caspases	785
17.2.3.3	Activation of Effector Caspases	785
17.2.3.4	Control by Inhibitor Proteins	785
17.2.3.5	Caspase Substrates	786
17.3	The Family of Bcl-2 Proteins: Gatekeepers of Apoptosis	786
17.4	The Mitochondrial Pathway of Apoptosis	789
17.4.1	Permeabilization of the Mitochondrial Outer Membrane	789
17.4.2	Formation of the Apoptosome and Triggering of a Caspase Cascade	791
17.4.2.1	Other Apoptogenic Proteins Released from Mitochondria	792
17.5	Death Receptor-Triggered Apoptosis	792
17.5.1	The Fas/CD95 Signaling Pathway	794

17.5.2	Tumor Necrosis Factor-Receptor 1 and Apoptosis	795
17.6	Links of Apoptosis to Cellular Signaling Pathways	795
17.6.1	PI3 Kinase/Akt Kinase and Apoptosis	796
17.6.2	The Protein p53 and Apoptosis	797
17.6.2.1	Apoptotic Genes Activated by p53	798
17.6.2.2	Transcription-Independent Induction of Apoptosis by p53	799
	Questions	799
	References	799

Index 801