

Gerhard Krauss

Biochemistry of Signal Transduction and Regulation

Third, Completely Revised Edition



WILEY-VCH GmbH & Co. KGaA

Contents

Preface VI

1	The Regulation of Gene Expression	1
1.1	Regulation of Gene Expression: How and Where? A Schematic Overview	1
1.2	Protein-Nucleic Acid Interactions as a Basis for Specific Gene Regulation	3
1.2.1	Structural Motifs of DNA-binding Proteins	3
1.2.2	The Nature of the Specific Interactions in Protein-Nucleic Acid Complexes	9
1.2.3	The Role of the DNA Conformation in Protein-DNA Interactions	11
1.2.4	Structure of the Recognition Sequence and Quaternary Structure of DNA-binding Proteins	13
1.3	The Principles of Transcription Regulation	17
1.3.1	Elements of Transcription Regulation	17
1.3.2	Functional Requirements for Repressors and Transcriptional Activators	19
1.3.3	Mechanisms for the Control of the Activity of DNA-binding Proteins	20
1.3.3.1	Binding of Effector Molecules	21
1.3.3.2	Binding of Inhibitory Proteins	23
1.3.3.3	Modification of Regulatory Proteins	23
1.3.3.4	Changes in the Concentration of Regulatory DNA-binding Proteins	24
1.4	Regulation of Transcription in Eucaryotes	25
1.4.1	Overview of Transcription Initiation in Procaryotes	26
1.4.2	The Basic Features of Eukaryotic Transcription	28
1.4.3	The Eucaryotic Transcription Apparatus	30
1.4.3.1	Structure of the Transcription Start Site and Regulatory Sequences	30
1.4.3.2	Elementary Steps of Eucaryotic Transcription	32
1.4.3.3	Formation of a Basal Transcription Apparatus from General Transcription Factors and RNA Polymerase	33
1.4.3.4	Phosphorylation of RNA Polymerase II and the Onset of Transcription	36
1.4.3.5	TFIIH - a Pivotal Regulatory Protein Complex	38

1.4.4	Regulation of Eucaryotic Transcription by DNA-binding Proteins	39
1.4.4.1	The Structure of Eucaryotic Transcriptional Activators	39
1.4.4.2	Concerted Action of Transcriptional Activators and Coactivators in the Regulation of Transcription	41
1.4.4.3	Interactions with the Transcription Apparatus	45
1.4.5	Regulation of the Activity of Transcriptional Activators	45
1.4.5.1	The Principal Pathways for the Regulation of Transcriptional Activators	46
1.4.5.2	Phosphorylation of Transcriptional Activators	46
1.4.5.3	Heterotypic Dimerization	50
1.4.5.4	Regulation by Binding of Effector Molecules	52
1.4.6	Specific Repression of Transcription	52
1.4.7	Chromatin Structure and Transcription Activation	55
1.4.7.1	Transcriptional Activity and Histone Acetylation	58
1.4.7.2	Transcriptional Activity and Histone Methylation	62
1.4.7.3	Enhanceosomes	63
1.4.8	Methylation of DNA	65
1.5	Post-transcriptional Regulation of Gene Expression	68
1.5.1	Modifications at the 5' and 3' Ends of the Pre-mRNA	69
1.5.2	Formation of Alternative mRNA by Alternative Polyadenylation and by Alternative Splicing	70
1.5.3	Regulation via Transport and Splicing of Pre-mRNA	73
1.5.4	Stability of the mRNA	75
1.5.5	Regulation at the Level of Translation	78
1.5.5.1	Regulation by binding of protein to the 5' end of the mRNA	79
1.5.5.2	Regulation by Modification of Initiation Factors	80
2	The Regulation of Enzyme Activity	89
2.1	Enzymes as Catalysts	90
2.2	Regulation of Enzymes by Effector Molecules	91
2.3	Principal Features of Allosteric Regulation	93
2.4	Regulation of Enzyme Activity by Binding of Inhibitor and Activator Proteins	94
2.5	Regulation of Enzyme Activity by Phosphorylation	95
2.5.1	Regulation of Glycogen Phosphorylase by Phosphorylation	97
2.5.2	Regulation of Isocitrate Dehydrogenase (E. coli) by Phosphorylation	100
2.6	Regulation via the Ubiquitin-Proteasome Pathway	101
2.6.1	Components of the Ubiquitin System	102
2.6.2	Degradation in the Proteasome	207
2.6.3	Recognition of the Substrate in the Ubiquitin-Proteasome Degradation Pathway	108
2.6.4	Regulatory Function of Ubiquitin Conjugation and the Targeted Degradation of Proteins	110
2.7	Regulation of Proteins by Sumoylation	113

3	Structure and Function of Signal Pathways	225
3.1	General Function of Signal Pathways	2 25
3.2	Structure of Signaling Pathways	227
3.2.1	The Mechanisms of Intercellular Communication	227
3.2.2	Principles of Intracellular Signal Transduction	2 29
3.2.3	Components of Intracellular Signal Transduction	220
3.2.4	Coupling of Proteins in Signaling Chains	222
3.2.4.1	Coupling by Specific Protein-Protein Interactions	222
3.2.4.2	Coupling by Protein Modules	222
3.2.4.3	Coupling by Reversible Docking Sites	223
3.2.4.4	Coupling by Colocalization	223
3.2.4.5	Linearity, Branching and Crosstalk	224
3.2.4.6	Variability and Specificity of Receptors and Signal Responses	126
3.3	Extracellular Signaling Molecules	228
3.3.1	The Chemical Nature of Hormones	228
3.3.2	Hormone Analogs: Agonists and Antagonists	232
3.3.3	Endocrine, Paracrine and Autocrine Signaling	233
3.3.4	Direct Modification of Protein by Signaling Molecules	233
3.4	Hormone Receptors	235
3.4.1	Recognition of Hormones by Receptors	235
3.4.2	The Interaction between Hormone and Receptor	235
3.5	Signal Amplification	239
3.6	Regulation of Inter- and Intracellular Signaling	242
3.7	Membrane Anchoring and Signal Transduction	242
3.7.1	Myristoylation	244
3.7.2	Palmitoylation	245
3.7.3	Farnesylation and Geranylation	246
3.7.4	The Glycosyl-Phosphatidyl-Inositol Anchor (GPI Anchor)	247
3.7.5	The Switch Function of Lipid Anchors	248
	Signaling by Nuclear Receptors	252
	Ligands of Nuclear Receptors	252
	Principles of Signaling by Nuclear Receptors	253
	Classification and Structure of Nuclear Receptors	256
	DNA-Binding Elements of Nuclear Receptors, HREs	256
	The DNA-Binding Domain of Nuclear Receptors	259
	HRE Recognition and Structure of the HRE-Receptor Complex	262
	Ligand-binding Domains	262
	Transactivating Elements of the Nuclear Receptors	264
	Mechanisms of Transcriptional Regulation by Nuclear Receptors	265
	Regulation and Variability of Signaling by Nuclear Receptors	269
	The Signaling Pathway of the Steroid Hormone Receptors	272
	Signaling by Retinoids, Vitamin D3, and the T3-Hormone	273
1,1	Structure of the HREs of RXR Heterodimers	275
	Complexity of the Interaction between HRE, Receptor and Hormone	275

5	C Protein-Coupled Signal Transmission Pathways 279
5.1	Transmembrane Receptors: General Structure and Classification 279
5.2	Structural Principles of Transmembrane Receptors 282
5.2.1	The Extracellular Domain of Transmembrane Receptors 282
5.2.2	The Transmembrane Domain 283
5.2.3	The Intracellular Domain of Membrane Receptors 285
5.2.4	Regulation of Receptor Activity 286
5.3	G Protein-Coupled Receptors 287
5.3.1	Structure of G Protein-Coupled Receptors 288
5.3.2	Ligand Binding 292
5.3.3	Mechanism of Signal Transmission 292
5.3.4	Switching Off and Desensitization of 7-Helix Transmembrane Receptors 292
5.3.5	Dimerization of GPCRs 296
5.4	Regulatory GTPases 297
5.4.1	The GTPase Superfamily: General Functions and Mechanism 297
5.4.2	Inhibition of GTPases by GTP Analogs 200
5.4.3	The G-domain as Common Structural Element of the GTPases 200
5.4.4	The Different GTPase Families 202
5.5	The Heterotrimeric G Proteins 202
5.5.1	Classification of the Heterotrimeric G Proteins 203
5.5.2	Toxins as Tools in the Characterization of Heterotrimeric G Proteins 205
5.5.3	The Functional Cycle of Heterotrimeric G Proteins 206
5.5.4	Structural and Mechanistic Aspects of the Switch Function of G Proteins 208
5.5.5	Structure and Function of the Py-Complex 225
5.5.6	Membrane Association of the G Proteins 227
5.5.7	Regulators of G Proteins: Phosducin and RGS Proteins 228
5.6	Effector Molecules of G Proteins 220
5.6.1	Adenylyl Cyclase and cAMP as Second Messenger 220
5.6.2	Phospholipase C 225
6	Intracellular Messenger Substances: Second Messengers 232
6.1	General Functions of Intracellular Messenger Substances 232
6.2	cAMP 233
6.3	cGMP 235
6.4	Metabolism of Inositol Phospholipids and Inositol Phosphates 237
6.5	Inositol 1,4,5-Triphosphate and Release of Ca^{2+} 240
6.5.1	Release of Ca^{2+} from Ca^{2+} Storage 242
6.5.2	Influx of Ca^{2+} from the Extracellular Region 245
6.5.3	Removal and Storage of Ca^{2+} 246
6.5.4	Temporal and Spatial Changes in Ca^{2+} Concentration 246
6.6	Phosphatidyl Inositol Phosphates and PI3-Kinase 248
6.6.1	PI3-Kinases 249
6.6.2	The Messenger Substance $\text{PtdIns}(3,4,5)\text{P}_3$ 250

6.6.3	Akt Kinase and PtdIns(3,4,5)P ₃ Signaling	252
6.6.4	Functions of PtdIns(4,5)P ₂	253
6.7	Ca ²⁺ as a Signal Molecule	253
6.7.1	Calmodulin as a Ca ²⁺ Receptor	256
6.7.2	Target Proteins of Ca ²⁺ /Calmodulin	257
6.7.3	Other Ca ²⁺ Receptors	258
6.8	Diacylglycerol as a Signal Molecule	259
6.9	Other Lipid Messengers	260
6.10	The NO Signaling Molecule	262
6.10.1	Reactivity and Stability of NO	262
6.10.2	Synthesis of NO	263
6.10.3	Physiological Functions and Attack Points of NO	264
7	Ser/Thr-specific Protein Kinases and Protein Phosphatases	269
7.1	Classification, Structure and Characteristics of Protein Kinases	269
7.1.1	General Classification and Function of Protein Kinases	269
7.1.2	Classification of Ser/Thr-specific Protein Kinases	272
7.2	Structure and Regulation of Protein Kinases	273
7.2.1	Main Structural Elements of Protein Kinases	274
7.2.2	Substrate Binding and Recognition	276
7.2.3	Control of Protein Kinase Activity	277
7.3	Protein Kinase A	280
7.3.1	Structure and Substrate Specificity of Protein Kinase A	280
7.3.2	Regulation of Protein Kinase A	282
7.4	Protein Kinase C	283
7.4.1	Characterization and Classification	283
7.4.2	Structure and Activation of Protein Kinase C	286
7.4.3	Regulation of Protein Kinase C	288
7.4.4	Functions and Substrates of Protein Kinase C	290
7.5	Ca²⁺/Calmodulin-dependent Protein Kinases	292
7.5.1	Importance and General Function	292
7.5.2	Structure and Auto regulation of CaM Kinase II	293
7.6	Ser/Thr-specific Protein Phosphatases	296
7.6.1	Structure and Classification of Ser/Thr Protein Phosphatases	296
7.6.2	Regulation of Ser/Thr Protein Phosphatases	297
7.6.3	Protein Phosphatase I, PPI	299
7.6.4	Protein Phosphatase 2A, PP2A	302
7.6.5	Protein Phosphatase 2B, Calcineurin	302
7.7	Regulation of Protein Phosphorylation by Subcellular Localization	305
8	Signal Transmission via Transmembrane Receptors with Tyrosine-Specific Protein Kinase Activity	322
8.1	Structure and Function of Receptor Tyrosine Kinases	322
8.1.1	General Structure and Classification	323
8.1.2	ligand Binding and Activation	324

8.1.3	Structure and Activation of the Tyrosine Kinase Domain	329
8.1.4	Effector Proteins of the Receptor Tyrosine Kinases	323
8.1.5	Attenuation and Termination of RTK Signaling	326
8.2	Protein Modules as Coupling Elements of Signal Proteins	328
8.2.1	SH2 Domains	329
8.2.2	Phosphotyrosine-binding Domain (PTB Domain)	332
8.2.3	SH3 Domains	332
8.2.4	Membrane-targeting Domains: Pleckstrin Homology (PH) Domains and FYVE Domains	334
8.2.5	Phosphoserine/Threonine-binding Domains	335
8.2.6	PDZ Domains	336
8.3	Nonreceptor Tyrosine-specific Protein Kinases	337
8.3.1	Structure and General Function of Nonreceptor Tyrosine Kinases	337
8.3.2	Src Tyrosine Kinase and Abl Tyrosine Kinase	338
8.4	Protein Tyrosine Phosphatases	342
8.4.1	Structure and Classification of Protein Tyrosine Phosphatases	343
8.4.2	Cooperation of Protein Tyrosine Phosphatases and Protein Tyrosine Kinases	346
8.4.3	Regulation of Protein Tyrosine Phosphatases	348
8.5	Adaptor Molecules of Intracellular Signal Transduction	352
9	Signal Transmission via Ras Proteins	355
9.1	The Ras Superfamily of Monomeric GTPases	355
9.2	General Importance of Ras Protein	358
9.3	Structure and Biochemical Properties of Ras Protein	360
9.3.1	Structure of the GTP- and GDP-bound Forms of Ras Protein	362
9.3.2	GTP Hydrolysis: Mechanism and Stimulation by GAP Proteins	363
9.3.3	Structure and Biochemical Properties of Transforming Mutants of Ras Protein	366
9.4	Membrane Localization of Ras Protein	366
9.5	GTPase-activating Protein (GAP) in Ras Signal Transduction	368
9.6	Guanine Nucleotide Exchange Factors (GEFs) in Signal Transduction via Ras Proteins	369
9.6.1	General Function of GEFs	369
9.6.2	Structure and Activation of GEFs	369
9.7	Raf Kinase as an Effector of Signal Transduction by Ras Proteins	373
9.7.1	Structure of Raf Kinase	373
9.7.2	Interaction of Raf Kinase with Ras Protein	374
9.7.3	Mechanism of Activation and Regulation of Raf Kinase	374
9.8	Reception and Transmission of Multiple Signals by Ras Protein	375
10	Intracellular Signal Transduction: the Protein Cascades of the MAP Kinase Pathways	383
10.1	Components of MAPK Pathways	385
10.2	The Major MAPK Pathways of Mammals	388

10.2.1	The ERK Pathway	388
10.2.2	The JNK/SAPK, p38 and ERK5 MAPK Pathways	392
11	Membrane Receptors with Associated Tyrosine Kinase Activity	395
11.1	Cytokines and Cytokine Receptors	395
11.2	Structure and Activation of Cytokine Receptors	396
11.2.1	Activation of Cytoplasmic Tyrosine Kinases	402
11.2.2	The Jak-Stat Pathway	405
11.2.2.1	The Janus Kinases	405
11.2.2.2	The Stat Proteins	406
11.3	T and B Cell Antigen Receptors	409
11.3.1	Receptor Structure	420
11.3.2	Intracellular Signal Molecules of the T and B Cell Antigen Receptors	422
11.4	Signal Transduction via Integrins	423
12	Other Receptor Classes	427
12.1	Receptors with Intrinsic Ser/Thr Kinase Activity: the TGF β Receptor and the Smad Proteins	427
12.1.1	TGF β Receptor	427
12.1.2	Smad Proteins	428
12.2	Receptor Regulation by Intramembrane Proteolysis	422
12.3	Signal Transduction via the Two-Component Pathway	424
13	Regulation of the Cell Cycle	429
13.1	Overview of the Cell Cycle	429
13.1.1	Principles of Cell Cycle Control	429
13.1.2	Intrinsic Control Mechanisms	432
13.1.3	External Control Mechanisms	433
13.1.4	Critical Cell Cycle Events and Cell Cycle Transitions	434
13.2	Key Elements of the Cell Cycle Apparatus	434
13.2.1	Cyclin-dependent Protein Kinases, CDKs	435
13.2.2	Structure of CDKs and Regulation by Phosphorylation	437
13.2.3	Cyclins	439
13.2.4	Regulation of Cyclin Concentration	440
13.2.5	Structural Basis for CDK Activation	442
13.2.6	Inhibitors of CDKs: the CKIs	445
13.2.7	Substrates of CDKs	447
13.2.8	Multiple Regulation of CDKs	449
13.3	Regulation of the Cell Cycle by Proteolysis	449
»3.1	Targeted Proteolysis by the SCF Complex	452
13.3.2	Proteolysis during Mitosis: the Anaphase-promoting Complex/Cytosome	452
13.4	The G $_2$ /S Phase Transition	453
13.4.1	Function of the D-type Cyclins	454
13.4.2	Function of pRb in the Cell Cycle	456
13.5	Cell Cycle Control of DNA Replication	462

13.6	The G ₂ /M Transition and Cdc25 Phosphatase	463
13.7	Summary of Cell Cycle Progression	465
13.8	The DNA Damage Checkpoints	466
14	Malfunction of Signaling Pathways and Tumorigenesis: Oncogenes and Tumor Suppressor Genes	469
14.1	General Aspects of Tumor Formation	469
14.1.1	Characteristics of Tumor Cells	469
14.1.2	Genetic Changes in Tumor Cells	472
14.1.3	Epigenetic Changes in Tumor Cells	472
14.1.4	Causes of Oncogenic Mutations	473
14.1.5	DNA Repair, DNA Damage Checkpoints, and Tumor Formation	474
14.1.6	Cell Division and Tumor Formation	475
14.2	Cell Division Activity, Errors in Function of Signal Proteins, and Tumor Formation	475
14.2.1	The Fate of a Cell: Quiescence, Division, or Death	476
14.3	Definition and General Function of Oncogenes and Tumor Suppressor Genes	477
14.3.1	Oncogenes and Proto-Oncogenes	478
14.3.2	Mechanisms of Activation of Proto-Oncogenes	479
14.3.3	Examples of the Functions of Oncogenes	482
14.4	Tumor Suppressor Genes: General Functions	487
14.5	DNA Repair, DNA Integrity and Tumor Suppression	488
14.6	The Retinoblastoma Protein pRb in Cancer	490
14.7	The p16 ^{INK4a} Gene Locus and ARF	493
14.8	The Tumor Suppressor Protein p53	494
14.8.1	Structure and Biochemical Properties of the p53 Protein	495
14.8.2	Sequence-Specific DNA Binding of p53	496
14.8.3	Genes Regulated by p53	498
14.8.4	Activation, Regulation and Modulation of the Function of p53	500
14.8.5	Overview of p53 Regulation	502
14.8.6	The MDM2-p53 Network and Cancer	505
14.9	The Tumor Suppressor APC and Wnt/P-Catenin Signaling	507
15	Apoptosis	522
15.1	Basic Functions of Apoptosis	522
15.2	Overview of Apoptosis	523
15.3	Caspases: Death by Proteolysis	525
15.4	The Family of Bel-2 Proteins: Gatekeepers of Apoptosis	520
> 15.5	The Mitochondrial Pathway of Apoptosis	522
15.6	Death Receptor-triggered Apoptosis	524
15.6.1	The Fas/CD95 Signaling Pathway	525
15.6.2	Tumor Necrosis Factor-Receptor 1 and Apoptosis	527
15.7	Links of Apoptosis and Cellular Signaling Pathways	528
15.7.1	PI3-Kinase/Akt Kinase and Apoptosis	529
15.7.2	The Protein p53 and Apoptosis	530
	Index	533