

Gerhard Krauss

**Biochemistry of Signal Transduction  
and Regulation**

**Second Edition**

Translated by Nancy Schönbrunner  
and Julia Cooper

 **WILEY-VCH**

Weinheim · New York · Chichester · Brisbane · Singapore · Toronto

Prof. Dr. Gerhard Krauss  
Laboratorium für Biochemie  
Universität Bayreuth  
D-95440 Bayreuth  
Germany  
e-mail: Gerhard.Krauss@uni-bayreuth.de



This book was carefully produced. Nevertheless, author and publisher do not warrant the information contained therein to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

1st English edition 1999  
2nd English edition 2001

Die Deutsche Bibliothek – CIP-Cataloguing-in-Publication-data  
A catalogue record for this publication is available from  
Die Deutsche Bibliothek

© Wiley-VCH Verlag GmbH, D-69469 Weinheim (Federal Republic of Germany), 2001

Printed on acid-free paper

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

Composition: Mitterweger & Partner Kommunikationsgesellschaft mbH, D-68723 Plankstadt  
Printing: betz-druck GmbH, D-64291 Darmstadt  
Bookbinding: Wilh. Osswald & Co., D-67433 Neustadt/Weinstr.

Printed in the Federal Republic of Germany

# Contents

420

455

473

495

## Chapter 1

### The Regulation of Gene Expression

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 . . . . .	4
1.2.1.1	Helix-Turn-Helix Motif. . . . .	5
1.2.1.2	Binding Motifs with Zinc Ions . . . . .	6
1.2.1.3	Basic Leucine Zipper and Helix-Loop-Helix Motifs . . . . .	10
1.2.1.4	DNA-binding via $\beta$ -Sheet Structures . . . . .	12
1.2.1.5	Flexible Structures in DNA-binding Proteins . . . . .	12
1.2.2	The Nature of the specific Interactions in Protein-Nucleic Acid	
	Complexes. . . . .	13
1.2.2.1	H-bonds in Protein-Nucleic Acid Complexes. . . . .	13
1.2.2.2	Ionic Interactions . . . . .	16
1.2.2.3	Van der Waals Contacts . . . . .	16
1.2.3	The Role of the DNA Conformation in Protein-DNA Interactions . . . .	17
1.2.3.1	Local Conformational Changes of DNA . . . . .	17
1.2.3.2	Bending of DNA . . . . .	18
1.2.4	Structure of the Recognition Sequence and Quarternary Structure	
	of DNA-binding Proteins . . . . .	21
1.3	The Principles of Transcription Regulation . . . . .	24
1.3.1	General Mechanism. . . . .	24
1.3.1.1	Elements of Transcription Regulation . . . . .	24
1.3.1.2	Negative Regulation of Transcription. . . . .	25
1.3.1.3	Positive Regulation of Transcription . . . . .	25
1.3.1.4	Functional Requirements for Repressors and Transcriptional activators .	26
1.3.2	Mechanisms for the Control of the Activity of DNA-binding Proteins . .	27
1.3.2.1	Binding of Effector Molecules . . . . .	27
1.3.2.2	Metal Ions as Effector Molecules . . . . .	30
1.3.2.3	Binding of Inhibitory Proteins . . . . .	31
1.3.2.4	Modification of Regulatory Proteins . . . . .	31
1.3.2.5	Changes in the Concentration of Regulatory DNA-binding Proteins . . .	34

1.4	Regulation of Transcription . . . . .	35
1.4.1	Overview of Transcription Initiation in Procaryotes . . . . .	35
1.4.1.2	s70-Dependent Transcription . . . . .	36
1.4.1.3	s54-dependent Promoters . . . . .	38
1.4.2	Structure of the Eucaryotic Transcription Apparatus . . . . .	39
1.4.2.1	Structure of the Transcription Start Site and Regulatory Sequences . . . . .	40
1.4.2.2	Elementary Steps of Eucaryotic Transcription . . . . .	41
1.4.2.3	Formation of a Basal Transcription Apparatus from General Initiation Factors and RNA Polymerase . . . . .	42
1.4.2.4	Phosphorylation of RNA Polymerase II and the Onset of Transcription . . . . .	45
1.4.2.5	TFIIH-A Pivotal Regulatory Protein Complex? . . . . .	46
1.4.3	Regulation of Eucaryotic Transcription by DNA-binding Proteins . . . . .	47
1.4.3.1	The Structure of Eucaryotic Transcriptional activators . . . . .	47
1.4.3.2	Concerted Action of Transcriptional activators and Co-activators in the Regulation of Transcription . . . . .	49
1.4.3.3	Interactions with the Transcription Apparatus . . . . .	52
1.4.4	Regulation of the Activity of Transcriptional activators . . . . .	53
1.4.4.1	The Principal Pathways for the Regulation of Transcriptional activators . . . . .	53
1.4.4.2	Phosphorylation of Transcriptional activators . . . . .	54
1.4.4.3	Heterotypic Dimerization . . . . .	58
1.4.4.4	Regulation by Binding of Effector Molecules . . . . .	59
1.4.5	Specific Repression of Transcription . . . . .	60
1.4.6	Chromatin Structure and Transcription Activation . . . . .	62
1.4.6.1	Transcriptional Activity and Histone Acetylation . . . . .	64
1.4.7	Methylation of DNA . . . . .	66
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 . . . . .	70
1.5.3	Alternative Splicing . . . . .	71
1.5.4	Regulation via Transport and Splicing of pre-mRNA . . . . .	73
1.5.5	Stability of the mRNA . . . . .	76
1.5.6	Regulation at the Level of Translation . . . . .	79
1.5.6.1	Regulation by Binding of Protein to the 5'-End of the mRNA . . . . .	79
1.5.6.2	Regulation by Modification of Initiation Factors . . . . .	80
1.5.6.3	Regulation of Translation via Insulin . . . . .	83

## **Chapter 2**

### **The Regulation of Enzyme Activity**

2.1	Enzymes as Catalysts . . . . .	89
2.2	Regulation of Enzymes by Effector Molecules . . . . .	90
2.3	Mechanistic Descriptions of Allosteric Regulation . . . . .	92

.....	35
.....	35
.....	36
.....	38
.....	39
quences . . . .	40
.....	41
l Initiation . . . .	42
transcription . . . .	45
.....	46
oteins . . . . .	47
.....	47
rators in the . . . .	49
.....	52
.....	53
al activators . . . .	53
.....	54
.....	58
.....	59
.....	60
.....	62
.....	64
.....	66
.....	68
.....	69
ation . . . . .	70
.....	71
.....	73
.....	76
.....	79
TA . . . . .	79
.....	80
.....	83
.....	89
.....	90
.....	92

2.4	Structural Basis of Allosteric Regulation on the Example of Phosphofructokinase . . . . .	94
2.5	Regulation of Enzyme Activity by Binding of Inhibitor and Activator Proteins . . . . .	98
2.6	Regulation of Enzyme Activity by Phosphorylation . . . . .	100
2.6.1	Regulation of Glycogen Phosphorylase by Phosphorylation . . . . .	101
2.6.2	Regulation of Isocitrate Dehydrogenase (E. coli) by Phosphorylation . . . . .	103
2.7	Regulation of Enzyme Activity by Proteolysis . . . . .	104
2.7.1	Maturation of Proteins via Proteolysis . . . . .	105
2.7.2	Specific Degradation of Proteins in the --ba--Ubiquitin- Proteasome“ Pathway . . . . .	107
2.7.2.1	Components of the Ubiquitin System . . . . .	108
2.7.2.2	Degradation in the Proteasome . . . . .	111
2.7.2.3	Recognition of the Substrate in the Ubiquitin-Proteasome Degradation Pathway . . . . .	112
2.7.2.4	Regulatory Function of Ubiquitin Conjugation and the Targeted Degradation of Proteins . . . . .	113

### Chapter 3

#### Function and Structure of Signaling Pathways

3.1	General Function of Signaling Pathways . . . . .	119
3.2	Structure of Signaling Pathways . . . . .	121
3.2.1	The Principle Mechanisms of Intercellular Communication . . . . .	121
3.2.2	Components of the Intracellular Signal Transduction . . . . .	123
3.3	Extracellular Signaling Molecules . . . . .	125
3.3.1	The Chemical Nature of Hormones . . . . .	125
3.3.2	Hormone Analogs: Agonists and Antagonists . . . . .	129
3.3.3	Endocrine, Paracrine and Autocrine Signaling. . . . .	129
3.3.4	Direct Modification of Protein by Signaling Molecules . . . . .	132
3.4	Hormone Receptors . . . . .	132
3.4.1	Recognition of Hormones by Receptors. . . . .	132
3.4.2	The Interaction between Hormone and Receptor . . . . .	134
3.4.3	Variability of the Receptor and Signal Response in the Target Cell . . . .	136
3.5	Signal Amplification . . . . .	137
3.6	Regulation of Inter- and Intracellular Signaling . . . . .	139

3.7	Membrane Anchoring and Signal Transduction . . . . .	141
3.7.1	Myristoylation . . . . .	143
3.7.2	Palmitoylation . . . . .	144
3.7.3	Farnesylation and Geranylation . . . . .	144
3.7.4	The Glycosyl-Phosphatidyl-Inositol Anchor (GPI Anchor) . . . . .	144

## **Chapter 4**

### **Signaling by Nuclear Receptors**

4.1	Ligands of Nuclear Receptors . . . . .	148
4.2	Principles of Signaling by Nuclear Receptors . . . . .	153
4.3	Classification and Structure of Nuclear Receptors . . . . .	155
4.3.1	DNA Binding Elements of Nuclear Receptors, HREs. . . . .	155
4.3.2	The DNA Binding Domain of Nuclear Receptors . . . . .	159
4.3.3	HRE Recognition and Structure of the HRE-Receptor Complex . . . . .	160
4.3.4	Ligand Binding Domains . . . . .	162
4.3.5	Transactivating Elements of the Nuclear Receptors . . . . .	162
4.4	The Signaling Pathway of the Steroid Hormone Receptors . . . . .	163
4.4.1	Activation of the Cytoplasmic Apo-Receptor Complexes. . . . .	163
4.4.2	DNA Binding and Transactivation . . . . .	165
4.4.3	Transcription Repression by Steroid Hormone Receptors . . . . .	166
4.4.4	Regulation of the Receptor Activity by Phosphorylation: Crosstalk . . . . .	166
4.5	Signaling by Retinoids, Vitamin D3, and the T3-Hormone. . . . .	167
4.5.1	The Structure of the HREs of RXR-Heterodimers. . . . .	168
4.5.2	Complexity of the Interaction between HRE, Receptor and Hormone . . . . .	169
4.5.3	Ligand Binding, Activation and Corepression of the RXR-Heterodimers . . . . .	170

## **Chapter 5**

### **G-protein Coupled Signal Transmission Pathways**

5.1	Transmembrane Receptors: General Structure and Classification . . . . .	173
5.2	Structural Principles of Transmembrane Receptors . . . . .	175
5.2.2	The Transmembrane Domain. . . . .	177
5.2.3	The Intracellular Domain of Membrane Receptors . . . . .	179
5.2.4	Regulation of Receptor Activity . . . . .	180

.....	141
.....	143
.....	144
.....	144
.....	144
.....	148
.....	153
.....	155
.....	155
.....	159
.....	160
.....	162
.....	162
.....	163
.....	163
.....	165
.....	166
.....	166
.....	167
.....	168
.....	169
.....	170
.....	173
.....	175
.....	177
.....	179
.....	180

5.3	G-protein Coupled Receptors . . . . .	181
5.3.1	Structure of G-Protein Coupled Receptors . . . . .	181
5.3.2	Ligand Binding. . . . .	183
5.3.3	Mechanism of Signal Transmission . . . . .	183
5.3.4	Switching off and Desensitization of G-Protein Coupled Receptors . . . .	184
5.4	Regulatory GTPases . . . . .	187
5.4.1	The GTPase Superfamily: General Functions and Mechanism . . . . .	187
5.4.2	Inhibition of GTPases by GTP Analogs . . . . .	189
5.4.3	The G-Domain as Common Structural Element of the GTPases . . . . .	190
5.4.4	The Different GTPase Families . . . . .	191
5.5	The Heterotrimeric G-Proteins . . . . .	192
5.5.1	Classification of the Heterotrimeric G-Proteins . . . . .	192
5.5.2	Toxins as Tools in Characterization of Heterotrimeric G-proteins . . . . .	195
5.5.3	The Functional Cycle of Heterotrimeric G-Proteins . . . . .	196
5.5.4	Mechanistic Aspects of the Switch Function of G-Proteins . . . . .	199
5.5.5	Mechanism of GTP Hydrolysis . . . . .	199
5.5.6	Structural Basis of the Activation of the $\alpha$ -Subunit . . . . .	202
5.5.7	Function of the $\beta\gamma$ -Complex . . . . .	204
5.5.8	Membrane Association of the G-Proteins . . . . .	205
5.5.9	Regulators of G-Proteins: Phosducin and RGS Proteins . . . . .	205
5.6	Effector Molecules of G-Proteins . . . . .	207
5.6.1	Adenylyl Cyclase and cAMP as "Second Messenger" . . . . .	207
5.6.2	Phospholipase C . . . . .	211

## Chapter 6

### Intracellular Messenger Substances: "Second Messengers"

6.1	General Functions of Intracellular Messenger Substances . . . . .	216
6.2	cAMP. . . . .	217
6.3	cGMP. . . . .	219
6.4	Metabolism of Inositol Phospholipids and Inositol Phosphate. . . . .	220
6.5	Inositol 1,4,5-Triphosphate and Release of $\text{Ca}^{2+}$ . . . . .	223
6.5.1	Release of $\text{Ca}^{2+}$ from $\text{Ca}^{2+}$ Storage . . . . .	225
6.5.2	Influx of $\text{Ca}^{2+}$ from the Extracellular Region. . . . .	227
6.5.3	Removal and Storage of $\text{Ca}^{2+}$ . . . . .	227
6.5.4	Temporal and Spatial Changes in $\text{Ca}^{2+}$ Concentration . . . . .	227

6.6	Phosphatidyl Inositol Phosphate and PI3-Kinase . . . . .	228
6.6.1	PI3-Kinases . . . . .	228
6.6.2	The Messenger Substance PtdIns(3,4,5)P3 . . . . .	231
6.6.3	Functions of PtdIns(4,5)P2 . . . . .	232
6.7	Ca <sup>2+</sup> as a Signal Molecule . . . . .	232
6.7.1	Calmodulin as a Ca <sup>2+</sup> Receptor . . . . .	234
6.7.2	Target proteins of Ca <sup>2+</sup> /Calmodulin . . . . .	236
6.7.3	Other Ca <sup>2+</sup> Receptors . . . . .	236
6.8	Diacylglycerol as a Signal Molecule . . . . .	237
6.9	Other Lipid Messengers . . . . .	237
6.10	The NO Signal Molecule . . . . .	239
6.10.1	Reactivity and Stability of NO . . . . .	239
6.10.2	Synthesis of NO . . . . .	240
6.10.3	Physiological Functions and Attack Points of NO . . . . .	241

## **Chapter 7**

### **Ser/Thr-specific Protein Kinases and Protein Phosphatases**

7.1	Classification, Structure and Characteristics of Ser/Thr-specific Protein Kinases . . . . .	247
7.1.1	General Classification and Function of Protein Kinases . . . . .	247
7.1.2	Classification of Ser/Thr-specific Protein Kinases . . . . .	249
7.1.3	Substrate Specificity of Ser/Thr-specific Protein Kinases . . . . .	250
7.1.4	The Catalytic Domain of Ser/Thr-specific Protein Kinases . . . . .	251
7.1.5	Autoinhibition and Intrasteric Regulation of Ser/Thr-specific Protein Kinases . . . . .	254
7.2	Protein Kinase A . . . . .	256
7.2.1	Structure and Substrate Specificity of Protein Kinase A . . . . .	256
7.2.2	Regulation of Protein Kinase A . . . . .	257
7.3	Protein Kinase C . . . . .	259
7.3.1	Characterization and Classification . . . . .	259
7.3.2	Structure and Activation of Protein Kinase C . . . . .	261
7.3.3	Regulation of Activity of Protein Kinase C . . . . .	263
7.3.4	Functions of Protein Kinase C . . . . .	265
7.4	Ca <sup>2+</sup> /calmodulin Dependent Protein Kinases . . . . .	266
7.4.1	Importance and General Function . . . . .	266
7.4.2	Structure and Autoregulation of CaM Kinase II . . . . .	267



.....	228
.....	228
.....	231
.....	232
.....	232
.....	234
.....	236
.....	236
.....	237
.....	237
.....	239
.....	239
.....	240
.....	241
ases	
ific	
.....	247
.....	247
.....	249
.....	250
.....	251
c Protein	
.....	254
.....	256
.....	256
.....	257
.....	259
.....	259
.....	261
.....	263
.....	265
.....	266
.....	266
.....	267

7.5	Ser/Thr-specific Protein Phosphatases . . . . .	270
7.5.1	Structure and Classification of Ser/Thr Protein Phosphatases . . . . .	270
7.5.2	Function and Regulation of Ser/Thr-specific Protein Phosphatases. . . . .	273
7.6	Coordinated Action of Protein Kinases and Protein Phosphatases . . . . .	274
7.6.1	Protein Phosphorylation and Regulation of Glycogen Metabolism. . . . .	275
7.6.2	Protein Phosphatase I and Regulation of Glycogen Metabolism . . . . .	277
7.7	Regulation of Protein Phosphorylation by Specific Localization at Subcellular Structures . . . . .	279
7.8	General Principles of Regulation of Enzymes by Phosphorylation and Dephosphorylation . . . . .	282

## Chapter 8

### Signal Transmission via Transmembrane Receptors with Tyrosine-specific Protein Kinase Activity

8.1	Structure and Function of Receptor Tyrosine Kinases . . . . .	286
8.1.1	General Structure and Classification . . . . .	288
8.1.2	Ligand Binding and Activation . . . . .	289
8.1.3	Structure and Activation of the Tyrosine Kinase Domain. . . . .	293
8.1.4	Effector Proteins of the Receptor Tyrosine Kinases . . . . .	296
8.2	Protein Modules as Coupling Elements of Signal Proteins . . . . .	298
8.2.1	SH2 Domains. . . . .	299
8.2.1.1	Binding Specificity and Structure of SH2 Domains. . . . .	300
8.2.1.2	Function of the SH2 Domain. . . . .	302
8.2.2	Phosphotyrosine Binding Domain, PTB Domain . . . . .	305
8.2.3	SH3 Domains. . . . .	306
8.2.3.1	SH3 Structure and Ligand Binding . . . . .	306
8.2.3.3	Functions of the SH3 Domain . . . . .	306
8.2.4	Pleckstrin Homology Domains. . . . .	308
8.2.5	PDZ Domains . . . . .	308
8.2.6	WW Domains. . . . .	309
8.3	Nonreceptor Tyrosine-specific Protein Kinases . . . . .	309
8.3.1	Structure and General Function of Nonreceptor Tyrosine Kinases . . . . .	310
8.3.2	Src Tyrosine Kinase and Abl Tyrosine Kinase . . . . .	310
8.4	Protein Tyrosine Phosphatases . . . . .	312
8.4.1	Structure and Classification of Protein Tyrosine Phosphatases. . . . .	313
8.4.2	Cooperation of Protein Tyrosine Phosphatases and Protein Tyrosine Kinases. . . . .	315
8.4.3	Regulation of Protein Tyrosine Phosphatases . . . . .	318
8.5	Adaptor Molecules of Intracellular Signal Transduction. . . . .	319

## **Chapter 9**

### **Signal Transmission via Ras Proteins**

9.1	General Importance and Classification of Ras Proteins . . . . .	324
9.2	Structure and Biochemical Properties of Ras Protein . . . . .	327
9.2.1	Structure of the GTP- and GDP-bound Forms of Ras Protein . . . . .	327
9.2.2	GTP Hydrolysis: Mechanism and Stimulation by GAP Proteins . . . . .	328
9.2.3	Structure and Biochemical Properties of Transforming Mutants of Ras Protein . . . . .	333
9.3	Membrane Localization of Ras Protein . . . . .	334
9.4	GTPase-activating Protein (GAP) in Ras Signal Transduction . . . . .	335
9.4.1	Structure of Ras-GAP Protein . . . . .	335
9.4.2	Function of Ras-GAP Protein . . . . .	336
9.5	Guanine Nucleotide Exchange Factors (GEFs) in Signal Transduction via Ras Proteins . . . . .	336
9.5.1	Importance of GEFs . . . . .	337
9.5.2	Structure and Activation of GEFs . . . . .	338
9.6	Raf Kinase as an Effector of Signal Transduction by Ras Proteins . . . . .	340
9.6.1	Structure of Raf Kinase . . . . .	340
9.6.2	Interaction of Raf Kinase with Ras Protein . . . . .	341
9.6.3	Mechanism of Activation and Regulation of Raf Kinase . . . . .	342
9.7	Reception and Transmission of Multiple Signals by Ras Protein . . . . .	343

## **Chapter 10**

### **Intracellular Signal Transduction: the Protein Cascades of the MAP Kinase Pathways**

10.1	Components of the MAPK Pathway . . . . .	352
10.2	Input Signals and Substrates of the MAPK Pathways . . . . .	354
10.3	The JNK Signaling Cascade . . . . .	356

**Chapter 11****Membrane Receptors with Associated Tyrosine Kinase Activity**

11.1	Cytokines and Cytokine Receptors . . . . .	358
11.1.1	Structure and Function of Cytokine Receptors. . . . .	359
11.1.2	Activation of Cytoplasmic Tyrosine Kinases . . . . .	362
11.1.3	The Jak-Stat Pathway . . . . .	364
11.1.3.1	The Janus Kinases . . . . .	364
11.1.3.2	The Stat Proteins. . . . .	365
11.2	T and B cell Antigen Receptors . . . . .	369
11.2.1	Receptor Structure . . . . .	369
11.2.2	Intracellular Signal Molecules of the T and B Cell Antigen Receptors. . . . .	371
11.3	Signal Transduction via Integrins. . . . .	371

**Chapter 12****Other Receptor Classes**

12.1	Receptors with Intrinsic Ser/Thr Kinase Activity: the TGF $\beta$ Receptor and the Smad Proteins . . . . .	377
12.1.1	TGF $\beta$ Receptor. . . . .	377
12.1.2	Smad Proteins. . . . .	379
12.2	Notch: Signaling with Protease Participation . . . . .	380
12.3	Signal Transduction via the Two-component Pathway . . . . .	380

**Chapter 13****Regulation of the Cell Cycle**

13.1	Overview of the Cell Cycle . . . . .	385
13.1.1	Principles of Cell Cycle Control . . . . .	386
13.1.2	Intrinsic Control Mechanisms. . . . .	388
13.1.3	External Control Mechanisms . . . . .	388
13.1.4	Critical Cell Cycle Events and Cell Cycle Transitions . . . . .	390
13.2	Key elements of the Cell Cycle Apparatus . . . . .	390
13.2.1	Cyclin-dependent Protein Kinases, CDKs. . . . .	391
13.2.2	Activation and Inactivation of CDKs by Phosphorylation . . . . .	391
13.2.3	Cyclins . . . . .	394

13.2.4	Stability of Cyclins . . . . .	396
13.2.5	Structural Basis for CDK Activation . . . . .	396
13.2.6	Inhibitors of CDKs, the CKIs . . . . .	398
13.2.7	Substrates of CDKs . . . . .	401
13.2.8	Multiple Regulation of CDKs . . . . .	403
13.3	Regulation of the Cell Cycle by Proteolysis . . . . .	403
13.3.1	Targeted Proteolysis at G1/S . . . . .	404
13.3.2	Proteolysis during Mitosis: the Anaphase-promoting Complex/ Cyclosome . . . . .	405
13.4	The G1/S phase Transition . . . . .	406
13.4.1	Function of the D Type Cyclins . . . . .	406
13.4.2	Function of pRb in the Cell Cycle . . . . .	408
13.4.3	Model of pRb Function . . . . .	409
13.5	Cell Cycle Control of DNA Replication . . . . .	412
13.6	The G2/M Transition and Cdc25 Phosphatase . . . . .	415
13.7	The DNA Damage Checkpoint . . . . .	416

## **Chapter 14**

### **Malfunction of Signaling Pathways and Tumorigenesis: Oncogenes and Tumor Suppressor Genes**

14.1	General Comments on Tumor Formation . . . . .	420
14.1.1	Characteristics of Tumor Cells . . . . .	420
14.1.2	Genetic Changes in Tumor Cells . . . . .	420
14.1.3	Changes in Methylation Pattern . . . . .	421
14.1.4	Causes of Oncogenic Mutations . . . . .	421
14.1.5	DNA Repair and Tumor Formation . . . . .	422
14.1.6	Cell Division and Tumor Formation . . . . .	423
14.2	Cell Division Activity, Errors in Function of Signal Proteins and Tumor Formation . . . . .	423
14.2.1	The Fate of a Cell: Division, Non-division or Death . . . . .	424
14.2.2	Definition and General Function of Oncogenes and Tumor Suppressor Genes . . . . .	425
14.2.3	Cellular Systems for Investigation of the Function of Oncogenes and Tumor Suppressor Genes . . . . .	427
14.3	Oncogenes and Proto-oncogenes . . . . .	428
14.3.1	Mechanisms of Activation of Proto-oncogenes . . . . .	428
14.3.1.1	Activation by Structural Changes . . . . .	428

.....	396
.....	396
.....	398
.....	401
.....	403
.....	403
.....	404
ex/.....	405
.....	406
.....	406
.....	408
.....	409
.....	412
.....	415
.....	416

## Oncogenes

.....	420
.....	420
.....	420
.....	421
.....	421
.....	422
.....	423
s and.....	423
.....	424
Suppressor.....	425
genes.....	427
.....	428
.....	428
.....	428

14.3.1.2	Activation by Concentration Increase .....	430
14.3.2	Examples of Functions of Proto-oncogenes and Oncogenes .....	432
14.4	Tumor Suppressor Genes .....	436
14.4.1	General Functions of Tumor Suppressor Genes .....	436
14.4.2	DNA Repair, DNA Integrity and Tumor Suppression .....	437
14.4.3	The Retinoblastoma Protein pRb as a Tumor Suppressor Protein. ....	438
14.4.4	The p16ink4a Gene Locus and Tumor Suppression .....	441
14.4.5	The Tumor Suppressor Protein p53 .....	441
14.4.5.1	Structure and Biochemical Properties of the p53 Protein .....	442
14.4.5.2	Sequence-specific DNA Binding of p53 .....	443
14.4.5.3	p53-regulated Genes .....	445
14.4.5.4	Activation, Regulation and Modulation of the Function of p53 .....	447
14.4.5.5	Model of p53 Function .....	450
14.4.6	Other Tumor Suppressor Genes .....	452

## Chapter 15 Apoptosis

15.1	Basic Functions of Apoptosis .....	456
15.2	Apoptosis in the Nematode <i>Caenorhabditis elegans</i> .....	457
15.3	Components of the Apoptotic Program in Mammals .....	458
15.3.1	Caspases: Death by Proteolysis .....	458
15.3.2	The Family of Bcl-2 Proteins .....	463
15.3.3	Cofactors of Caspase Activation .....	464
15.3.4	Intracellular Regulation .....	465
15.4	Stress-mediated Apoptosis: the Cytochrome c/Apaf1 Pathway. ....	465
15.5	Death-receptor-triggered Apoptosis. ....	467
15.6	Apoptosis and Cellular Signaling Pathways .....	469

## Chapter 16 Ion Channels and Signal Transduction

16.1	Principles of Neuronal Communication .....	473
16.2	Membrane Potential and Electrical Communication .....	474

XXII *Overview of Chapters*

16.3	Structure and Function of Voltage-gated Ion Channels . . . . .	476
16.3.1	Principles of Regulation of Ion Channels . . . . .	476
16.3.2	Characteristics of Voltage-gated Ion Channels . . . . .	477
16.3.3	Structure of Voltage-gated Ion Channels . . . . .	478
16.3.4	Structural Basis of Ion Channel Function . . . . .	480
16.3.5	Voltage-dependent Activation . . . . .	480
16.3.6	Ion Passage and Pore Walls . . . . .	482
16.3.7	Inactivation of Voltage-gated Ion Channels . . . . .	482
16.4	Ligand-gated Ion Channels . . . . .	483
16.4.1	Neurotransmitters and Mechanisms of Ligand-gated Opening of Ion Channels . . . . .	483
16.4.2	Neurotransmitter-controlled Receptors with Intrinsic Ion Channel Function . . . . .	486
16.4.2.1	The NMDA Receptor . . . . .	487
16.4.2.2	The Nicotinic Acetylcholine Receptor . . . . .	489
	Subject Index . . . . .	495