HANDBOOK OF (**) Cell Signaling

Volume 1

Editors-in-Chief

RALPH A. BRADSHAW

EDWARD A. DENNIS



Contents

VOLUME 1		Prospects References	
Contributors xlv reface lxvii CHAPTER 1 Cell Signaling: Yesterday, Today, and Comorrow alph A. Bradshaw and Edward A. Dennis Origins of Cell Signaling Inter Polypeptide Growth Factors Cell Signaling at the Molecular Level Lipid Signaling Cell Signaling Cell Signaling Tomorrow Ceferences	1	CHAPTER 3 Computational Genomics: Prediction of Protein Functional Linkages and Networks Todd O. Yeates and Michael J. Thompson Introduction Approaches to Analyzing Protein Functions on a Genome-Wide Scale Current Issues and Future Prospects for Computing Functional Interactions References	1:
PART I NITIATION: EXTRACELLULAR AND MEMBRANE EVENTS ames Wells, Editor		CHAPTER 4 Molecular Sociology Irene M. A. Nooren and Janet M. Thornton Transmembrane Signaling Paradigms Structural Basis of Protein—Protein Recognition Conclusion References	2:
Section A: Molecular Recognition Ian Wilson, Editor CHAPTER 2 Structural and Energetic Basis of Molecular Recognition mil Alexov and Barry Honig introduction rinciples of Binding Monspecific Association with Membrane Surfaces rotein—Protein Interactions	11	CHAPTER 5 Free Energy Landscapes in Protein—Protein Interactions Jacob Piehler and Gideon Schreiber Introduction Thermodynamics of Protein—Protein Interactions Interaction Kinetics The Transition State Association of a Protein Complex Dissociation of a Protein Complex Summary References	2*

CHAPTER 6 Antibody-Antigen Recognition and Conformational Changes Robyn L. Stanfield and Ian A. Wilson	33	CHAPTER 11 T-Cell Receptor/pMHC Complexes Markus G. Rudolph and Ian A. Wilson TCR Generation and Architecture	63
Introduction Antibody Architecture Conformational Changes Conclusion References		Peptide Binding to MHC Class I and II TCR/pMHC Interaction Conclusions and Future Perspectives References	
CHAPTER 7 Binding Energetics in Antigen— Antibody Interfaces Roy A. Mariuzza Introduction Thermodynamic Mapping of Antigen— Antibody Interfaces Conclusions References	39	CHAPTER 12 Mechanistic Features of Cell-Surface Adhesion Receptors Steven C. Almo, Anne R. Bresnick, and Xuewu Zhang Mechanosensory Mechanisms Cell-Cell Adhesions/Adherens Junctions T-Cell Costimulation Axon Guidance and Neural Development Conclusions References	74
CHAPTER 8 Immunoglobulin-Fc Receptor Interactions Brian J. Sutton, Rebecca L. Beavil, and Andrew J. Beavil Introduction IgG-Receptor Interactions IgE-Receptor Interactions Summary References	45	CHAPTER 13 The Immunological Synapse Michael L. Dustin Introduction Migration and the Immunological Synapse The Cytoskeleton and the Immunological Synapse The Role of Self MHCp in T-Cell Sensitivity to Foreign MHCp Integration of Adaptive and Innate Responses Summary References	79
CHAPTER 9 Plasticity of Fc Recognition Warren L. DeLano Introduction Structures of the Natural Fc Binding Domains The Consensus Binding Site on Fc Evolution of an Fc Binding Peptide Factors Promoting Plasticity Conserved and Functionally Important Molecular Interactions Conclusion	51	CHAPTER 14 NK Receptors Roland K. Strong Introduction Immunoreceptors Natural Killer Cells Ig-Type NK Receptors: KIR C-Type Lectin-Like NK Receptors: Ly49A C-Type Lectin-Like NK Receptors: NKG2D References	83
Chapter 10 Ig-Superfold and Its Variable Uses in Molecular Recognition Nathan R. Zaccai and E. Yvonne Jones Introduction The Immunoglobulin Superfamily Ig-Superfold-Mediated Recognition References	57	CHAPTER 15 Carbohydrate Recognition and Signaling James M. Rini and Hakon Leffler Introduction Biological Roles of Carbohydrate Recognition Carbohydrate Structure and Diversity Lectins and Carbohydrate Recognition Carbohydrate-Mediated Signaling Conclusions References	87

CHAPTER 16 Rhinovirus—Receptor Interactions Elizabeth Hewat	95	Concluding Remarks References CHAPTER 22	
References		Structures of Heterotrimeric G Proteins	
CHAPTER 17 HIV-1 Receptor Interactions	99	and Their Complexes Stephen R. Sprang Introduction	127
Peter D. Kwong Molecular Interactions Atomic Details Recognition in the Context of a Humoral Immune Response References		Gα Subunits Ga-Effector Interactions GTP Hydrolysis by Gα and Its Regulation by RGS Proteins Gβγ Dimers GPR/GoLoco Motifs Gα-GPCR Interactions	
CHAPTER 18 Influenza Virus Neuraminidase Inhibitors Garry L. Taylor	105	References Section B: Vertical Receptors Henry Bourne, Editor	
Introduction Flu Virus: Role of NA Structure of NA Active Site Inhibitor Development Conclusion References		CHAPTER 23 Structure and Function of G-Protein-Coupled Receptors: Lessons from the Crystal Structure of Rhodopsin Thomas P. Sakmar	139
CHAPTER 19 Signal Transduction and Integral Membrane Proteins Geoffrey Chang and Christopher B. Roth	115	Introduction Introduction to Rhodopsin: a Prototypical G-Protein-Coupled Receptor Molecular Structure of Rhodopsin Molecular Mechanism of Receptor Activation References	
Introduction Electrophysiology: Rapid Signal Transduction Mechanosensation: How Do We Feel? Active Transporters: Rapid Response and Energy Management Receptors: Gate Keepers for Cell Signaling		CHAPTER 24 Human Olfactory Receptors Orna Man, Tsviya Olender, and Doran Lancet References	145
CHAPTER 20 Structural Basis of Signaling Events Involving Fibrinogen and Fibrin Russell F. Doolittle References	119	CHAPTER 25 Chemokines and Chemokine Receptors: Structure and Function Carol J. Raport and Patrick W. Gray Introduction Chemokine Structure and Function Chemokine Receptors	149
CHAPTER 21 Structural Basis of Integrin Signaling Robert C. Liddington Introduction Structure Quaternary Changes Tertiary Changes	123	CHAPTER 26 The Binding Pocket of G-Protein-Coupled Receptors for Biogenic Amines, Retinal, and Other Ligands Lei Shi and Jonathan A. Javitch	155
Tail Interactions		Introduction	

The Binding Pocket of GPCRs A Role of the Second Extracellular Loop in Ligand Binding References CHAPTER 27 Glycoprotein Hormone Receptors: A Unique Paradigm for Ligand Binding and GPCR Activation Gilbert Vassart, Marco Bonomi, Sylvie Claeysen, Cedric Govaerts, Su-Chin Ho, Leonardo Pardo, Guillaume Smits, Virginie Vlaeminck, and Sabine Costagliola	161	CHAPTER 31 Agonist-Induced Desensitization and Endocytosis of G-Protein- Coupled Receptors Mark von Zastrow Introduction General Processes of GPCR Regulation Mechanisms of GPCR Desensitization and Endocytosis Functional Consequences of GPCR Endocytosis References	181
Introduction Molecular Pathophysiology Structure Function Relationships of the Glycoprotein Hormone Receptors Conclusions and Perspectives References		CHAPTER 32 Functional Role(s) of Dimeric Complexes Formed from G-Protein- Coupled Receptors Marta Margeta-Mitrovic and Lily Yuh Jan	187
CHAPTER 28		References	
Protease-Activated Receptors Shaun R. Coughlin Introduction Mechanisms of Activation Protease-Activated Receptor Family Roles of PARs In Vivo References	167	CHAPTER 33 The Role of Chemokine Receptors in HIV Infection of Host Cells Jacqueline D. Reeves and Robert W. Doms Introduction HIV Entry	191
CHAPTER 29 Constitutive and Regulated Signaling in Virus-Encoded 7TM Receptors Thue Schwartz Virus-Encoded Proteins Are Developed through	173	Coreceptor Use In Vivo Env Domains Involved in Coreceptor Interactions Coreceptor Domains Involved in HIV Infection Receptor Presentation and Processing Role of Signaling in HIV Infection Summary References	
Targeted Evolution In Vivo The Redundant Chemokine System Is an Optimal Target for Viral Exploitation Multiple Virus-Encoded 7TM Receptors Constitutive Signaling through Altered Pathways Viral Receptors Recognize Multiple Ligands with Variable Function		CHAPTER 34 Chemotaxis Receptor in Bacteria: Transmembrane Signaling, Sensitivity, Adaptation, and Receptor Clustering Weiru Wang and Sung-Hou Kim	197
Attempts to Identify the Function of Virus-Encoded Receptors In Vivo References CHAPTER 30 Frizzleds as G-Protein-Coupled Receptors		Signaling at Periplasmic Ligand Binding Domain Signaling at the Cytoplasmic Domain Adaptation Clustering of the Chemoreceptor and Sensitivity Future Studies References	
for Wnt Ligands Sarah H. Louie, Craig C. Malbon, Randall T. Moon Introduction Wnt Signaling Evidence for Frizzleds as G-Protein- Coupled	177	CHAPTER 35 Overview: Function and Three- Dimensional Structures of Ion Channels Daniel L. Minor, Jr.	203
Receptors Perspective References		Introduction Studies of Full-Length Ion Channels General Pore Features Revealed by Bacterial Channels	s

Pore Helices: Electrostatic Aids to Permeation Open Channels Eukaryotic Ion Channels at High Resolution: Divide and Conquer Ion Channel Accessory Subunits: Soluble		CHAPTER 41 Regulation of Ion Channels by Direct Binding of Cyclic Nucleotides Edgar C. Young and Steven A. Siegelbaum	233
and Transmembrane The Future: Ion Channels as Electrosomes References		Introduction The Cyclic Nucleotide-Gated Channels Other Channels Directly Regulated by Cyclic Nucleotides	
Chapter 36		References	
How Do Voltage-Gated Channels Sense			
the Membrane Potential? Chris S. Gandhi and Ehud Y. Isacoff	209	Section C: Horizontal Receptors Robert Stroud, Editor	
Introduction The Voltage-Sensing Gating Particle S4 Is the Primary Voltage Sensor Physical Models of Activation: Turning a Screw through a Bolt Coupling Gating to S4 Voltage-Sensing Motions References		CHAPTER 42 Overview of Cytokine Receptors Robert M. Stroud	239
CHAPTER 37 Ion Permeation: Mechanisms of Ion Selectivity and Block Bertil Hille Aqueous Pore	215	CHAPTER 43 Growth Hormone and IL-4 Families of Hormones and Receptors: The Structural Basis for Receptor Activation and Regulation Anthony A. Kossiakoff	241
Ion Selectivity Block References		Introduction The Growth Hormone Family of Hormones and Receptors	
CHAPTER 38 Agonist Binding Domains of Glutamate Receptors: Structure and Function Mark L. Mayer	219	Structural Basis for Receptor Homodimerization Hormone Specificity and Cross-Reactivity Determine Physiological Roles Hormone-Receptor Binding Sites Receptor-Receptor Interactions Hormone-Receptor Binding Energetics	
References		Biological Implications of Transient	
CHAPTER 39 Nicotinic Acetylcholine Receptors Arthur Karlin	223	Receptor Dimerization A High-Affinity Variant of hGH (hGH _v) Reveals an Altered Mode for Receptor Homodimerization Site1 and Site2 Are Structurally and	
Function Structure References		Functionally Coupled IL-4 Hormone-Induced Receptor Activation IL-4-α-Chain Receptor Interface	
CHAPTER 40 Small Conductance Ca ²⁺ -Activated K ⁺ Channels: Mechanism of Ca ²⁺ Gating	227	Binding of the γ-Chain Receptor Comparisons of IL-4 with GH(PRL) Concluding Remarks References	
John P. Adelman	:	CHARRED 44	
Introduction Clones Encoding SK Channels Biophysical and Pharmacological Profiles Mechanisms of Ca ²⁺ -gating		CHAPTER 44 Erythropoietin Receptor as a Paradigm for Cytokine Signaling Deborah J. Stauber, Minmin Yu, and Ian A. Wilson	251
Pantophobiac After All References		Introduction Biochemical Studies Supporting Preformed Dimers	

			
Other Cytokine Receptor Superfamily Members Conclusions References		Ligand-Receptor Complexes Consequences of Ligand-Receptor Complex Formation	
CHAPTER 45 A New Paradigm of Cytokine Action		Receptor Preassociation Conclusion References	
Revealed by Viral IL-6 Complexed to gp130: Implications for GCSF Interaction with GCSFR Dar-chone Chow, Lena Brevnova, Xiao-lin He, and K. Christopher Garcia	259	CHAPTER 49 The Mechanism of NGF Suggested by the NGF-TrkA-D5 Complex Abraham M. de Vos and Christian Wiesmann	281
Introduction Receptor/Ligand Interactions The gp130 System Viral Interleukin-6 GCSF and GCSFR Structure of the Viral IL-6–gp130 Complex		Introduction Neurotrophins Trks NGF-TrkA-D5 Complex p75 ^{NTR} References	
Site 1 The Site 2 Interface The Site 3 Interface Implications of the vIL-6-gp130 Tetramer Structure for the Active GCSF-GCSFR Extracellular Signaling Complex		CHAPTER 50 The Mechanism of VEGFR Activation Suggested by the Complex of VEGF-flt1-D2 Christian Wiesmann and Abraham M. de Vos	285
CHAPTER 46 The Fibroblast Growth Factor (FGF) Signaling Complex Fen Wang and Wallace L. McKeehan	265	Introduction Heparin-Binding Domain of VEGF Receptor-Binding Domain VEGF VEGF Receptors VEGF-flt1-D2 Complex References	
Introduction FGF Polypeptides FGFR Tyrosine Kinases Heparan Sulfate Oligomeric FGF-FGFR-HS Signaling Complex Intracellular Signal Transduction by the FGFR Complex Pafarances		CHAPTER 51 Receptor–Ligand Recognition in the TGFβ Family as Suggested by the Crystal Structures of BMP-2–BR-IA _{ec} and TGFβ3–TR-II _{ec} Matthias K. Dreyer	289
CHAPTER 47 Structure of IFN-γ and Its Receptors Mark R. Walter References	271	Introduction Ligand and Receptor Structures Receptor-Ligand Complexes BMP-2-BR-IA _{ec} Complex Complex Formation with TGFβ Is Different than for BMP-2 References	
CHAPTER 48 Structure and Function of Tumor Necrosis Factor at the Cell Surface Stephen R. Sprang	275	CHAPTER 52 Insulin Receptor Complex and Signaling by Insulin Lindsay G. Sparrow and S. Lance Macaulay	293
Introduction Structure of Tumor Necrosis Factor TNF Receptors Extracellular (Ligand Binding) Domains of TNF Family Receptors		Introduction Insulin Receptor Domain Structure Binding Determinants of the IR Insulin Signaling to Glucose Transport References	

CHAPTER 53 Structure and Mechanism of the Insulin Receptor Tyrosine Kinase Steven R. Hubbard Introduction Structural/Mechanistic Studies Prospects	299	CD40 Signaling Is Mediated by TRAF-Dependent and TRAF-Independent Pathways References CHAPTER 58 Role of Lipid Domains in EGF Receptor Signaling Linda J. Pike	323
References CHAPTER 54 What Does the Structure of Apo2L/ TRAIL Bound to DR5 Tell Us About Death Receptors? Sarah G. Hymowitz and Abraham M. de Vos Introduction	305	Introduction Localization of the EGF Receptor to Lipid Rafts Rafts and EGF-Receptor-Mediated Signaling The EGF Receptor and Caveolin Summary References CHAPTER 59	
Novel Features in the Structure of Apo2L/TRAIL Apo2L/TRAIL:DR5 Structures Ligand-Independent Receptor Assembly Intracellular Consequences of Ligand Binding Conclusion References Section D: Membrane Proximal Even Tom Alber, Editor	ents	Structure and Function of B-Cell Antigen Receptor Complexes Michael Reth and Michael Huber Introduction The Structure of the B Cell Antigen Receptor Initiation of BCR Signaling Is Controlled by Redox Regulation References CHAPTER 60	327
CHAPTER 55 TNF Receptor Associated Factors Jee Y. Chung, Young Chul Park, Hong Ye, and Hao Wu References CHAPTER 56	311	Lipid-Mediated Localization of Signaling Proteins Maurine E. Linder Introduction Protein Lipidation Summary References	331
Assembly of Signaling Complexes for TNF Receptor Family Molecules Gail A. Bishop and Bruce S. Hostager	315	CHAPTER 61 G-Protein Organization and Signaling Maria R. Mazzoni and Heidi E. Hamm	335
Introduction Receptor Aggregation Raft Recruitment Ubiquitination Receptor Interactions Conclusions References CHAPTER 57		Introduction G-Protein Molecular Organization Structural Features of G Protein Activation Structural Determinants of Receptor— G-Protein Specificity Gα Interactions with Effector Molecules Gβγ Interactions with Effector Molecules Conclusions References	
Mechanisms of CD40 Signaling in the Immune System Aymen Al-Shamkhani, Martin J. Glennie, and Mark S. Cragg	319	CHAPTER 62 JAK-STAT Signaling Rashna Bhandari and John Kuriyan	343
Introduction Signaling Pathways Triggered by CD40 Engagement		Introduction Cytokine Signaling Proteins JAK Structure and Localization	

STAT Structure and Function Inhibition of Cytokine Signaling Summary		Section A: Protein Phosphorylation Tony Pawson	n
CHAPTER 63 Organization of Photoreceptor Signaling Complexes Susan Tsunoda INAD Organizes Signaling Complexes INAD-Signaling Complexes in Phototransduction Assembly, Targeting, and Anchoring of Signaling	349	CHAPTER 66 Eukaryotic Kinomes: Genomic Cataloguing of Protein Kinases and Their Evolution Tony Hunter and Gerard Manning Introduction The Yeasts: Saccharomyces cerevisiae and Schizosaccharomyces pombe	373
Complexes Signaling Complexes in Vertebrate Photoreceptors References		Nematodes: Caenorhabditis elegans Insects: Drosophila melanogaster Vertebrates: Homo sapiens Comparative Kinomics	
Chapter 64		Coda References	
Protein Localization in Negative Signaling Jackson G. Egen and James P. Allison	355	<u>CHAPTER 67</u> Modular Protein Interaction Domains	
Introduction The Role of CD28 and CTLA-4 in T-Cell Activation Expression and Localization of CTLA-4 and CD28: Consequences for Receptor Function Mechanisms of CTLA-4-Mediated Negative Signaling Conclusions References CHAPTER 65 Transmembrane Receptor Oligomerization Darren Tyson and Ralph A. Bradshaw Introduction Tyrosine Kinase-Containing Receptors Cytokine Receptors Guanylyl Cyclase-Containing Receptors Serine/Threonine Kinase-Containing Receptors Tumor Necrosis Factor Receptors	3 61	in Cellular Communication Tony Pawson and Piers Nash Introduction Phosphotyrosine-Dependent Protein— Protein Interactions Interaction Domains: A Common Theme in Signaling Adaptors, Pathways, and Networks Evolution of a Phospho-Dependent Docking Protein Multisite Phosphorylation, Ubiquitination, and Switch-Like Responses Summary References CHAPTER 68 Structures of Serine/Threonine and Tyrosine Kinases Matthew A. Young and John Kuriyan	379
Heptahelical Receptors (G-Protein-Coupled Receptors) Concluding Remarks References		Introduction Structures of Protein Kinases Structures of Inactive Protein Kinases Summary References CHAPTER 69	
PART II TRANSMISSION: EFFECTORS AND CYTOSOLIC EVENTS Tony Hunter, Editor	ND	Protein Tyrosine Kinase Receptor Signaling Overview Carl-Henrik Heldin Introduction PTK Subfamilies	391
PART II Introduction Tony Hunter, Editor	369	Mechanism of Activation Control of PTK Receptor Activity Cross-Talk Between Signaling Pathways	

PTK Receptors and Disease References		Eph Receptors and Cell Adhesion Ephrin Reverse Signaling	
CHAPTER 70		EphrinB Reverse Signaling Via Phosphotyrosine EphrinB Reverse Signaling Via PDZ	٠
Signaling by the Platelet-Derived		Domain Interactions	
Growth Factor Receptor Family	397	Summary References	
M. V. Kovalenko and Andrius Kazlauskas		References	
Introduction		Chapter 74	
Platelet-Derived Growth Factors, Their		Cytokine Receptor Superfamily	
Receptors, and Assembly of the PDGF		Signaling	427
Receptor Signaling Complex		James N. Ihle	72/
Some Aspects of Regulation of the PDGF			
Receptor-Initiated Signaling		Cytokine Receptor Superfamily Signaling	
References		References	
CHAPTER 71		CHAPTER 75	
EGF Receptor Family	405	Negative Regulation of the JAK/STAT	
Mina D. Marmor and Yosef Yarden	405	Signaling Pathway	431
		Joanne L. Eyles and Douglas J. Hilton	
Introduction		Introduction	
Domain Structure of ErbBs		The Phosphatases	
Subcellular Localization of ErbB Proteins		STAT Phosphatases	
ErbB-Induced Signaling Pathways Negative Regulatory Pathways		PIAS (Protein Inhibitors of Activated STATS)	
Specificity of Signaling Through the ErbB Network		SOCS (Suppressors of Cytokine Signaling) Family	
ErbB Proteins and Pathological Conditions		Concluding Comments	
References		References	
Cova person 72		CHAPTER 76	
CHAPTER 72		Activation of Oncogenic Protein Kinases	441
IRS-Protein Scaffolds and Insulin/IGF		G. Steven Martin	441
Action	409		
Morris F. White		Introduction	
IRS-Proteins: The Beginnings		Physiological Regulation of Protein Kinases Activation of Protein Kinases by Retroviruses	
IRS-Proteins and Insulin Signaling		Activation of Protein Kinases by Renoviruses Activation of Protein Kinases in Human Cancer	
IRS-Protein Structure and Function		Oncogenic Protein Kinases as Targets for Therapy	
IRS-Protein Signaling in Growth, Nutrition,		References	
and Longevity			
Interleukin-4 and IRS2 Signaling		CHAPTER 77	
Heterologous Regulation of IRS-Protein Signals		Protein Kinase Inhibitors	451
IRS2 and Pancreatic β-Cells		Alexander Levitzki	
Summary			
References		Signal Transduction Therapy	
Chapter 73		Protein Tyrosine Kinase Inhibitors SER/THR Kinase Inhibitors	
Eph Receptors	421	References	
Rüdiger Klein		Cramma 70	
Tutuodustian		<u>Chapter 78</u>	
Introduction Ephs and Ephrins		Integrin Signaling: Cell Migration,	
Eph Receptor Signaling Via Cytoplasmic Protein		Proliferation, and Survival	463
Tyrosine Kinases		J. Thomas Parsons, Jill K. Slack-Davis, and	
Eph Receptor Signaling Via Rho Family GTPases		Karen H. Martin	
Effects on Cell Proliferation		Introduction	
Eph Receptor Signaling through PDZ-Domain-		Integrins Nucleate the Formation of Multi-	
Containing Proteins		Protein Complexes	ev.

·			
Cell Migration: A Paradigm for Studying Integrin Signaling Integrin Regulation of Cell Proliferation and Surv Links to Cancer	vival:	CHAPTER 83 MAP Kinases James R. Woodgett	493
Concluding Remarks References CHAPTER 79 Downstream Signaling Pathways: Modular Interactions Bruce J. Mayer Introduction General Properties of Interaction Modules Roles in Signaling	471	Introduction The ERK Module Stress-Activated MAPKs, Part 1: SAPK/JNKs Stress-Activated MAPKs, Part 2: p38 MAPKs MAPKKs MAPKKKs MAPKKKs Summary References	
Prospects References CHAPTER 80		CHAPTER 84 Cytoskeletal Regulation: Small G-Protein–Kinase Interactions Ed Manser	499
Non-Receptor Protein Tyrosine Kinases in T-Cell Antigen Receptor Function Kiminori Hasegawa, Shin W. Kang, Chris Chiu and Andrew C. Chan Introduction	475	Introduction P21-Activated Kinases Myotonic Dystrophy Kinase-Related Cdc42- Binding Kinase Rho-Associated Kinase (ROK) References	
T-Cell Antigen Receptor Structure Src PTKs Csk (c-Src PTK) ZAP-70/Syk PTKs Tec PTKs Summary		CHAPTER 85 Recognition of Phospho- Serine/Threonine Phosphorylated Proteins Stephen J. Smerdon and Michael B. Yaffe	505
CHAPTER 81 Cbl: A Physiological PTK Regulator Wallace Y. Langdon Introduction	483	Introduction 14-3-3 Proteins FHA Domains WW Domains Leucine-Rich Repeats and WD40 Domains Concluding Remarks References	
Domains of Cbl Proteins Sli-1: A Negative Regulator of RPTKs PTK Downregulation by Polyubiquitylation Cbl-Deficient Mice Future Directions References		CHAPTER 86 Role of PDK1 in Activating AGC Protein Kinase Dario R. Alessi	513
CHAPTER 82 FGFβ Signal Transduction Jeffrey L. Wrana John Smad Pathway John Smad Pathway John Smad Independent Signaling Pathways John Receptor Interaction Proteins	487	Introduction Mechanisms of Activation of PKB PKB Is Activated by PDK1 Activation of Other Kinases by PDK1 Phenotype of PDK1 PKB- and S6K-Deficient Mice and Model Organisms Hydrophobic Motif of AGC Kinases Mechanisms of Regulation of PDK1 Activity Structure of the PDK1 Catalytic Domain Concluding Remarks	

CHAPTER 87 Regulation of Cell Growth and Proliferation in Metazoans by mTOR and the p70 S6 Kinase Joseph Avruch	523	CHAPTER 92 Protein Kinase C: Relaying Signals from Lipid Hydrolysis to Protein Phosphorylation Alexandra C. Newton	551
Introduction Functions of TOR Signaling from TOR Regulation of mTOR Activity References		Introduction Protein Kinase C Family Regulation of Protein Kinase C Function of Protein Kinase C Summary References	
CHAPTER 88 AMP-Activated Protein Kinase D. Grahame Hardie	535	CHAPTER 93 The PIKK Family of Protein Kinases Graeme C. M. Smith and Stephen P. Jackson	557
Introduction Structure of the AMPK Complex Regulation of the AMPK Complex Regulation in Intact Cells and Physiological Targets Medical Implications of the AMPK System References		Introduction Overview of PIKK Family Members Overall Architecture of PIKK Family Proteins MTOR: A Key Regulator of Cell Growth DNA-Pkes: At the Heart of the DNA	
CHAPTER 89 Principles of Kinase Regulation Bostjan Kobe and Bruce E. Kemp	539	Nonhomologous End-Joining Machinery ATM and ATR: Signalers of Genome Damage SMG-1: A Regulator of Nonsense-Mediated mRNA Decay	
Introduction Protein Kinase Structure General Principles of Control Regulatory Sites in Protein Kinase Domains Conclusions		TRRAP: A Crucial Transcriptional Co-Activator PIKK Family Members as Guardians of Nucleic Acid Structure, Function, and Integrity? References	
CHAPTER 90 Chapter 90		CHAPTER 94 Histidine Kinases	563
Calcium/Calmodulin-Dependent Protein Kinase II Mary B. Kennedy	543	Fabiola Janiak-Spens and Ann H. West References	
Introduction Structure of CaMKII Regulation by Autophosphorylation Regulatory Roles of CaMKII in Neurons References		CHAPTER 95 Atypical Protein Kinases: The EF2/MHCK/ChaK Kinase Family Angus C. Nairn	567
CHAPTER 91 Glycogen Synthase Kinase 3 Philip Cohen and Sheelagh Frame	547	Introduction Identification of an Atypical Family of Protein Kinases: EF2 Kinase, Myosin Heavy Chain Kinase and ChaK	
Introduction The Substrate Specificity of GSK3 The Regulation of GSK3 Activity by Insulin and Growth Factors GSK3 as a Drug Target The Role of GSK3 in Embryonic Development GSK3 and Cancer References		The Structure of the Atypical Kinase Domain Reveals Similarity to Classical Protein Kinases and to Metabolic Enzymes with ATP-Grasp Domains Substrate Specificity of Atypical Kinases Regulation of Atypical Kinases Functions of the Atypical Family of Protein Kinases References	

Chapter 96		<u>Chapter 101</u>	
Casein Kinase I and Regulation of the		The Structure and Topology of Protein	
Circadian Clock	575	Serine/Threonine Phosphatases	601
Saul Kivimäe, Michael W. Young, and Lino Saez		David Barford	001
Introduction		Introduction	
double-time: A Casein Kinase I Homolog in Drosophila		Protein Serine/Threonine Phosphatases of the	
Casein Kinase I in the Mammalian Clock		PPP Family Protein Serine/Threonine Phosphatases of the	
Casein Kinase I in the Neurospora Clock		PPM Family	
Similarities and Differences of CKI Function in		Conclusions	
Different Clock Systems		References	
References			
CHAPTER 97		CHAPTER 102	
The Leucine-Rich Repeat Receptor Protein	n	Naturally Occurring Inhibitors of Protein	
Kinases of Arabidopsis thaliana: A Paradig		Serine/Threonine Phosphatases	607
for Plant LRR Receptors	579	Carol MacKintosh and Julie Diplexcito	
John C. Walker and Kevin A. Lease		Introduction	
Introduction		Effects of Inhibitors in Cell-Based Experiments	
LRR Receptor Protein Kinases: The Genomic		The Toxins Bind to the Active Sites of Protein	
Point of View		Phosphatases Chemical Synthesis of Protein Phosphatase Inhibitors	
LRR Receptor Protein Kinases: The Functional View		Microcystin Affinity Chromatography and	
Summary References		Affinity Tagging	
References		Avoiding the Menace of Toxins in the Real World	
CHAPTER 98		Outside the Laboratory	
Engineering Protein Kinases with		References	
Specificity for Unnatural Nucleotides		CHAPPED 102	
and Inhibitors	583	CHAPTER 103	<i>(</i> 10
Chao Zhang and Kevan M. Shokat		Protein Phosphatase 1 Binding Proteins Anna A. Depaoli-Roach	613
References		•	
		Introduction Protein Phosphotoco 1 (PP1)	
Section B: Protein Dephosphorylation	on	Protein Phosphatase 1 (PP1) PP1 Regulatory or Targeting Subunits	
Jack E. Dixon, Editor		Conclusions	
		References	
CHAPTER 99			
Overview of Protein Dephosphorylation	591	Chapter 104	
Jack E. Dixon		Role of PP2A in Cancer and	
C 100		Signal Transduction	621
Chapter 100		Gernot Walter	
Protein Serine/Threonine Phosphatases	500	Introduction	
and the PPP Family Patricia T. W. Cohen	593	Structure of PP2A	
Current Classification of Protein Serine/Threonine		Subunit Interaction Association of PP2A with Cellular Proteins	
Phosphatases		Alteration or Inhibition of PP2A Is Essential	
Background		in Human Cancer Development	
Evolution and Conserved Features of the PPP Family		Mutation of Aα and Aβ Isoforms in Human Cancer	
Catalytic Activities of the PPP Family Members		Differences between Aα and Aβ Subunits	
Eukaryotic PPP Subfamilies Domain and Subunit Structure of PPP Family Member	re	PP2A and Wnt Signaling PP2A and MAP Kinase Pathway	
- omain and outdome of the raining McIlloc	LO	LI 2/1 and Mith Ishlast Falliway	

Summary

References

Medical Importance of the PPP Family

Chapter 105		PTPs and Human Disease	
Serine/Threonine Phosphatase		Perspectives	
Inhibitor Proteins	627	References	
Shirish Shenolikar	·-·	Creepon 100	-1
		<u>Chapter 109</u>	
Introduction		Protein Tyrosine Phosphatase Structure	
Protein Phosphatase 1 (PP1) Inhibitors			653
I-1, DARPP-32, and Other Phosphorylation- Dependent Phosphatase Inhibitors		Youngjoo Kim and John M. Denu	
Latent Phosphatase Complexes Activated by		Introduction	
Inhibitor Phosphorylation		Introduction to the Protein Tyrosine	
Inhibitors of Type-2 Serine/Threonine Phosphatases		Phosphatase Family	
Conclusions		Structure	
References		Mechanism	
		Regulation	
Chapter 106		References	
Calcineurin	631		
Claude B. Klee and Seun-Ah Yang		<u>Chapter 110</u>	
		Bioinformatics: Protein Tyrosine	
Introduction		Phosphatases	659
Enzymatic Properties Structure		Niels Peter H. Møller, Peter Gildsig Jansen,	
Regulation		Lars F. Iversen, and Jannik N. Andersen	
Distribution and Isoforms		Introduction to Bioinformatics	
Functions		Amino Acid Homology Among PTP Domains and	
Muscle Differentiation		Structure-Function Studies	
Conclusion		Identification of the Genomic Complement of PTPs	
References		Functional Aspects of PTPs in Health and Disease: Bioinformatics	
CHAPTER 107		References	
Protein Serine/Threonine-Phosphatase			
2C (PP2C)	637	<u>Chapter 111</u>	
Hisashi Tatabe and Kazuhiro Shiozaki		PTP Substrate Trapping	671
Introduction		Andrew J. Flint	
Regulation of the Stress-Activated MAP		Introduction	
Kinase Cascades		Original C→S and D→A Substrate-Trapping Mutants	
Control of the CFTR Chloride Channel by PP2C		Second-Generation Trapping Mutants	
Plant Hormone Abscisic Acid Signaling		Accessory or Noncatalytic Site Contributions to	
Fem-2: A Sex-Determining PP2C in		Substrate Recognition	
Nematode		New Twists on Trapping	
Stress-Responsive PP2Cs in Bacillus subtilis		Other Applications of Substrate Trapping Mutants	
References		References	
CHAPTER 108		<u>Chapter 112</u>	
Overview of Protein Tyrosine		Inhibitors of Protein Tyrosine	
Phosphatases	641	Phosphatases	677
Nicholas K. Tonks		Zhong-Yin Zhang	
Background		Introduction	
Structural Diversity within the PTP Family		Covalent PTP Modifiers	
The Classical PTPs		Oxyanions as PTP Inhibitors	
The Dual Specificity Phosphates (DSPs)		PTyr Surrogates as PTP Inhibitors	
Regulation of PTP Function		Bidentate PTP Inhibitors	
Oxidation of PTPs in Tyrosine Phosphorylation-		Other PTP Inhibitors	
Dependent Signaling		Concluding Remarks	
Substrate Specificity of PTPs		References	

MAPK Phosphatases in Drosophila

melanogaster

CHAPTER 113 Regulating Receptor PTP Activity Erica Dutil Sonnenburg, Tony Hunter, and	685	MAPK Phosphatases in Mammals Summary References	
Joseph P. Noel Introduction Regulation by Dimerization Regulation by Phosphorylation Regulation by D2 Domain		CHAPTER 118 SH2-Domain-Containing Protein— Tyrosine Phosphatases Benjamin G. Neel, Haihua Gu, and Lily Pao	707
References CHAPTER 114 CD45 Zheng Xu, Michelle L. Hermiston, and Arthur Weiss Introduction Structure Function	689	History and Nomenclature Structure, Expression, and Regulation Biological Functions of Shps Shp Signaling and Substrates Determinants of Shp Specificity Shps and Human Disease Summary and Future Disease References	
Regulation References		CHAPTER 119 Insulin Receptor PTP: PTP1B Alan Cheng and Michel L. Tremblay	729
CHAPTER 115 Properties of the Cdc25 Family of Cell-Cycle Regulatory Phosphatases William G. Dunphy	693	Introduction PTP1B as a Bona Fide IR Phosphatase PTP1B Gene Polymorphisms and Insulin Resistance	
Introduction Physiological Functions of Cdc25 Regulation of Cdc25 Concluding Remarks References		Insulin-Mediated Modulation of PTP1B Genetic Evidence for Other PTP1B Substrates Concluding Remarks References	
CHAPTER 116 Cell-Cycle Functions and Regulation of Cdc14 Phosphatases Harry Charbonneau	697	CHAPTER 120 Low-Molecular-Weight Protein Tyrosine Phosphatases Robert L. Van Etten	733
Introduction The Cdc14 Phosphatase Subgroup of PTPs Budding Yeast Cdc14 is Essential for Exit from Mitosis Fission Yeast Cdc14 Coordinates Cytokinesis with Mitosis Potential Cell-Cycle Functions of Human		Introduction Structures of LMW PTPases Catalytic Mechanism Inhibitors and Activators Substrate Specificity, Regulation, and Biological Role References	
Cdc14A and B References CHAPTER 117		CHAPTER 121 STYX/Dead-Phosphatases	741
MAP Kinase Phosphatases Marco Muda and Steve Arkinstall Introduction	703	Matthew J. Wishart Introduction Gathering Styx: Structure Implies Function The Gratefully Undead: STYX/Dead-Phosphatases Madiata Phospharulation Signaling	
MAPK Phosphatases in Yeast A MAPK Phosphatase in C. elegans		Mediate Phosphorylation Signaling Conclusions	

VOLUME 2		Molecular Properties of Ca ²⁺ Channels Molecular Basis for Ca ²⁺ Channel Function	
Contributors xlv		Ca ²⁺ Channel Regulation Conclusion	
<u>Part II</u> fransmission: effectors an cytosolic events (continue		Door of the contract of the co	31
FROM VOLUME 1) Section C: Calcium Mobilization	21.5	James W. Putney, Jr. Capacitative Calcium Entry Store-operated Channels	
Michael J. Berridge, Editor CHAPTER 122		Mechanism of Activation of Store-Operated Channels Summary References	
Phospholipase C Hong-Jun Liao and Graham Carpenter Introduction PLC Anatomy	5	CHAPTER 128 Arachidonic Acid-regulation Ca ²⁺ Channel Trevor J. Shuttleworth	35
PLC Activation Mechanisms PLC Physiology References		Introduction Identification and Characterization of ARC Channels Specific Activation of ARC Channels by Low Agonist Concentrations	
CHAPTER 123 Inositol 1,4,5-trisphosphate 3-kinase and 5-phosphatase Valérie Dewaste and Christophe Erneux	11	Roles of ARC Channels and SOC/CRAC Channels in [Ca ²⁺] _i Signals: "Reciprocal Regulation" Conclusions and Implications References	
Introduction Type I InsP ₃ 5-phosphatase InsP ₃ 3-kinase References		CHAPTER 129 IP ₃ Receptors Colin W. Taylor	41
CHAPTER 124 Cyclic ADP-ribose and NAADP Antony Galione and Grant C. Churchill	15	Introduction References CHAPTER 130	
Introduction References		Ryanodine Receptors David H. MacLennan and Guo Guang Du	45
CHAPTER 125 Sphingosine 1-phosphate Kenneth W. Young and Stefan R. Nahorski	19	Function and Structure Activation of Ryanodine Receptor Ca ²⁺ Release Channe Molecular Biology of Ryanodine Receptors References	els
Introduction Sphingolipid Metabolism Activation of SPHK Intracellular Target for SPP-mediated Ca ²⁺ Release Concluding Remarks		CHAPTER 131 Intracellular Calcium Signaling Martin D. Bootman, H. Llewelyn Roderick, Rodney O'Connor, and Michael J. Berridge	51
References CHAPTER 126 Voltage-gated Ca ²⁺ Channels William A. Catterall	23	The "Calcium Signaling Toolkit" and Calcium Homeosta Multiple Channels and Messengers Underlie Ca ²⁺ Increases Temporal Regulation of Ca ²⁺ Signals Spatial Regulation of Ca ²⁺ Signals	asis
Introduction Physiological Roles of Voltage-gated Ca ²⁺ Channels Ca ²⁺ Current Types Defined by Physiological and Pharmacological Properties		Modulation of Ca ²⁺ Signal Amplitude Ca ²⁺ as a Signal within Organelles and in the Extracellular Space References	

CHAPTER 132 Calcium Pumps Ernesto Carafoli Introduction Reaction Cycle of the SERCA and PMCA Pumps	57	Class C. Recoverins Class D. Guanylate Cyclase Activating Proteins Class E. K+ Channel Interacting Proteins Future Perspectives for the NCS Protein Family References	
The SERCA Pump The PMCA Pump Genetic Diseases Evolving Defects of Calcium Pumps References		CHAPTER 137 Calmodulin-Mediated Signaling Anthony R. Means	8.
CHAPTER 133		Introduction References	
Sodium/Calcium Exchange Mordecai P. Blaustein	63	CHAPTER 138	
Introduction Two Families of PM Na ⁺ /Ca ²⁺ Exchanges Modes of Operation of the Na ⁺ /Ca ²⁺ Exchangers		The Family of S100 Cell Signaling Proteins Claus W. Heizmann, Beat W. Schäfer, and Günter Fritz	87
Regulation of NCX Inhibition of NCX Localization of the NCX Physiological Roles of the NCX References		Introduction Protein Structures and Metal-Dependent Interactions with Target Proteins Genomic Organization, Chromosomal Localization, and Nomenclature	
CHAPTER 134 Ca ²⁺ Buffers Beat Schwaller	67	Translocation, Secretion, and Biological Functions Associations with Human Diseases Conclusion and Perspectives References	
Introduction Relevant Parameters for Ca ²⁺ Buffers Ca ²⁺ Buffers as One Component Contributing to Intracellular Ca ²⁺ Homeostasis		CHAPTER 139 C ₂ -Domains in Ca ²⁺ -Signaling Thomas C. Südhof and Josep Rizo	95
Biological Effects of Ca ²⁺ Buffers References		Structures of C ₂ -Domains Ca ²⁺ -Binding Mode of C ₂ -Domains Phospholipid Binding Mechanism of C ₂ -Domains	
CHAPTER 135 Mitochondria and Calcium Signaling, Point and Counterpoint	72	Other Ligands of C ₂ -Domains Functions of C ₂ -Domains References	
Michael R. Duchen	73	CHAPTER 140	101
Introduction Fundamentals Machinery of Michael 10, 2+ M		Annexins and Calcium Signaling Stephen E. Moss	101
Machinery of Mitochondrial Ca ²⁺ Movement The Set Point Quantitative Issues, Microdomains, and the Regulation [Ca ²⁺] _c Signals	of	Introduction Annexins as Ca ²⁺ Channel Regulators Conclusions References	
Impact of Ca ²⁺ Uptake on Mitochondrial Function Mitochondrial Ca ²⁺ , Disease, and Death CODA References		CHAPTER 141 Calpain Alan Wells and Anna Huttenlocher	105
CHAPTER 136		Introduction	
EF-Hand Proteins and Calcium Sensing: The Neuronal Calcium Sensors Jamie L. Weiss and Robert D. Burgoyne	79	Calpain Family Modes of Regulation Calpain as a Signaling Intermediate: Potential Targets	
Introduction Class A. Neuronal Calcium Sensor 1 (Frequenin) Class B. Neurocalcins (VII.IPs) and Hippocalcin		Functional Roles Future Considerations References	

CHAPTER 142 Regulation of Intracellular Calcium through Hydrogen Peroxide Sue Goo Rhee	113	CHAPTER 146 Phosphoinositide 3-Kinases David A. Fruman Introduction	135
Introduction Sources and Chemical Properties of ROS Activation of Ryanodine and IP ₃ Receptor Ca ²⁺ Release Channels by H ₂ O ₂ Enhancement of [Ca ²⁺] _i through H ₂ O ₂ -mediated Inactivation of Protein Tyrosine Phosphatase and PTEN		The Enzymes The Products Lipid-Binding Domains Effectors and Responses Phosphatases Genetics Summary	
References Section D: Lipid-Derived Second Messengers Lewis Cantley, Editor		CHAPTER 147 PTEN/MTM Phosphatidylinositol Phosphatases Knut Martin Torgersen, Soo-A Kim, and Jack E. Dixon	143
CHAPTER 143 Historical Overview: Protein Kinase C, Phorbol Ester, and Lipid Mediators Yasutomi Nishizuka and Ushio Kikkawa	119	PTEN Myotubularin: a Novel Family of Phosphatidylinositol Phosphatases References CHAPTER 148	l
Retrospectives of Phospholipid Research Protein Kinase C and Diacylglycerol Phorbol Ester and Cell Signaling Structural Heterogeneity and Mode of Activation Translocation and Multiple Lipid Mediators		SHIP Inositol Phosphate Phosphatases Larry R. Rohrschneider Introduction SHIP1 Structure, Expression, and Function SHIP2 Structure, Expression, and Function References	147
Conclusion References CHAPTER 144 Type I Phosphatidylinositol 4-phosphate		CHAPTER 149 Structural Principles of Lipid Second Messenger Recognition Roger L. Williams	153
5-kinases (PI4P 5-kinases) K. A. Hinchliffe and R. F. Irvine Introduction Basic Properties Regulation Function References	123	Introduction Phospholipid Second Messenger Recognition by Active Sites of Enzymes Phosphoinositide-binding Domains Non-phosphoinositide Lipid Messenger Recognition Future Directions References	
CHAPTER 145 Type 2 PIP4-Kinases Lucia Rameh	129	CHAPTER 150 Pleckstrin Homology (PH) Domains Mark A. Lemmon	161
Introduction History Structure Type 2 PIP4-Kinase Isoforms Regulation Putative Models for the Function of the Type 2 PIP-Kinases Conclusion References		Identification and Definition of PH Domains The Structure of PH Domains PH Domains as Phosphoinositide-Binding Modules Binding of PH Domains to Non-phosphoinositide Ligands Possible Roles of Non-phosphoinositide PH Ligands Conclusions References	

CHAPTER 151

PX Domains

Hui Liu and Michael B. Yaffe		Phosphoinositides	203
History and Overview of PX Domains		Sonja Krugmann, Len Stephens, and Phillip T. Hawkins	
Lipid-Binding Specificity and the Structure		Introduction	
of PX Domain		Rho Family Small GTPases	
Function of PX Domain-containing Proteins		Arf Family GTPases	
References		Modulation of Ras Family GTPases by PI3K	
CHAPTER 152		Conclusion References	
FYVE Domains in Membrane			
Trafficking and Cell Signaling	177	CHAPTER 156	
Christopher Stefan, Anjon Audhya, and Scott Emr			
-		Phosphoinositides and Actin Cytoskeletal	
Introduction		Rearrangement	209
Role for PtdIns(3)P in Membrane Trafficking and Identification of the FYVE Domain		Paul A. Janmey, Robert Bucki, and Helen L. Yin	
Structural Basis for the FYVE Domain		Historical Perspective	
Conservation of the FYVE Domain and Localization		Stimulating Cellular Actin Polymerization	
of PtdIns(3)P		Actin-Membrane Linkers Localized or Activated	
FYVE Domains in Membrane Trafficking		by PIP2	
FYVE Domains Involved in PtdIns(3)P Metabolism		Relation of Actin Assembly to Phsphoinositide-contain	ning
FYVE Domains in Signaling		Lipid Rafts	
FYVE-like Domains		Different Mechanisms of PPI-Actin Binding Protein	
Conclusions		Regulation	
References		Effects on Lipid Membrane Structure	
		References	
Chapter 153			
Protein Kinase C: Relaying Signals		CHAPTER 157	
from Lipid Hydrolysis to Protein		The Role of PI3 Kinase in Directional	
Phosphorylation	187	Sensing during Chemotaxis in <i>Dictyosteliui</i>	P2-2
Alexandra C. Newton			,,
		a Model for Chemotaxis of Neutrophils	015
Introduction		and Macrophages	217
Protein Kinase C Family		Richard A. Firtel and Ruedi Meili	
Regulation of Protein Kinase C Function of Protein Kinase C		Introduction	
Summary		Directional Movement	
References		Localization of Cytoskeletal and Signaling Componen	its
References		The Signaling Pathways Controlling	
CHAPTER 154		Directional Movement	
Role of PDK1 in Activating AGC		PI3K Effectors and their Roles in	
Protein Kinase	193	Controlling Chemotaxis	
Dario R. Alessi	193	The Tumor Suppressor PTEN Regulates the	
Dario K. Alessi		Chemoattractant PI3K Pathways Conclusions	
Introduction		References	
Mechanism of Activation of PKB		References	
PKB Is Activated by PDK1			
Activation of Other Kinases by PDK1		<u>Chapter 158</u>	
Phenotype of PDK1 PKB- and S6K-Deficient Mice an	na	Phosphatidylinositol Transfer Proteins	225
Model Organisms Hydrophobic Motif of AGC Vineses		Shamshad Cockcroft	
Hydrophobic Motif of AGC Kinases Machanism of Regulation of PDK1 Activity		Introduction	
Mechanism of Regulation of PDK1 Activity Structure of the PDK1 Catalytic Domain		The Classical PITPs: α and β	
Concluding Remarks		ine ciangical i i i i e w and D	
References		RdgB Family of PITP Proteins References	

CHAPTER 155

171

Modulation of Monomeric G Proteins by

CHAPTER 159 Inositol Polyphosphate Regulation of Nuclear Function John D. York	229	CHAPTER 164 SPC/LPC Receptors Linnea M. Baudhuin, Yijin Xiao, and Yan Xu Introduction	253
Introduction Inositol Signaling and the Molecular Revolution Links of Inositol Signaling to Nuclear Function The Inositol Polyphosphate Kinase (IPK) Family References		Physiological and Pathological Functions of LPC and SPC Identification of Receptors for SPC and LPC Perspectives References	
<u>Chapter 160</u>		<u>Chapter 165</u>	
Ins(1,3,4,5,6)P ₅ : A Signal		The Role of Ceramide in	
Transduction Hub Stephen B. Shears	233	Cell Regulation Yusuf A. Hannun and L. Ashley Cowart	257
Introduction References		Ceramide-Mediated CellR Biochemical Pathways of Ceramide Generation Ceramide Targets	
Chapter 161		Conclusions	
Phospholipase D	237	References	
Paul C. Sternweis		C 1//	
Tuess direct ou		<u>Chapter 166</u>	
Introduction Structural Domains and Requirements		Phospholipase A ₂ Signaling and	
for Activity		Arachidonic Acid Release	261
Catalysis: Mechansim and Measurement		Jesús Balsinde and Edward A. Dennis	
Modification of Mammalian PLDs		Introduction	
Regulatory Inputs for Mammalian PLD		PLA ₂ Groups	
Regulatory Pathways		Cellular Function	
Physiological Function of PA		Summary	
Localization of PLD		References	
Future Directions			
References		Chapter 167	
		Prostaglandin Mediators	265
<u>Chapter 162</u>		Emer M. Smyth and Garret A. Fitzgerald	203
Diacylglycerol Kinases	243		
M. K. Topham and S. M. Prescott		Introduction	
•		The Cyclooxygenase Pathway	
Introduction The DCK Femily		Prostanoid Receptors	
The DGK Family Regulation of DGKs		Thromboxane A ₂ (TxA ₂)	
Paradigms of DGK Function		Prostacyclin (PGI ₂) Prostaglandin D ₂ (PGD ₂)	
Conclusions		Prostaglandin E_2 (PGE ₂)	
References		Prostaglandin $F_{2\alpha}$ (PGF _{2\alpha})	
		Concluding Remarks	
Chapter 163		References	
	0.45		
Sphingosine-1-Phosphate Receptors	247	<u>Chapter 168</u>	
Michael Maceyka and Sarah Spiegel		Leukotriene Mediators	275
Introduction		Jesper Z. Haeggström and Anders Wetterholm	413
The S1PRs			
S1P Signaling via S1PRs		Introduction	
Transactivation of S1PRs		Five-Lipoxygenase	
Downstream Signaling from S1PRs		Leukotriene A ₄ Hydrolase	
References		References	, 3°

Isolation of Specific Proteomes

CHAPTER 169 Lipoxins and Aspirin-Triggered 15-epi- Lipoxins: Mediators in Anti-inflammation and Resolution Charles N. Serhan Lipoxin Signals in the Resolution of Inflammation Novel Anti-Inflammatory Signals and Pathways Consolution Remotes	281	Affinity Chromatography for the Isolation of Protein Complexes Specificity of Protein-Protein or Protein-Ligand Interact References CHAPTER 174 FRET Analysis of Signaling Events in Cells	ctions 305
Concluding Remarks References CHAPTER 170 Cholesterol Signaling Peter A. Edwards, Heidi R. Kast-Woelbern, and Matthew A. Kennedy	287	Peter J. Verveer and Philippe I. H. Bastiaens Introduction Fluorescent Probes for FRET FRET Detection Techniques Conclusions and Prospects References	
Introduction Cholesterol Precursors Cholesterol Cholesterol Derivatives: Ligands for Nuclear Receptor References Section E: Protein Proximity	rs	CHAPTER 175 Peptide Recognition Module Networks: Combining Phage Display with Two-Hybri Analysis to Define Protein-Protein Interactions Gary D. Bader, Amy Hin Yan Tong, Gianni Cesareni, Christopher W. Hogue, Stanley Fields, and Charles Boone	id 311
Interactions John D. Scott, Editor		Introduction References	
CHAPTER 171 Protein Proximity Interactions John D. Scott Introduction	293	CHAPTER 176 The Focal Adhesion: A Network of Molecular Interactions Benjamin Geiger, Eli Zamir, Yariv Kafri, and	317
Techniques for the Analysis of Protein-Protein Interact Subcellular Structures and Multiprotein Complexes Kinase and Phosphatase Targeting Proteins CHAPTER 172	tions	Kenneth M. Yamada Introduction Connectivity-Based Ordering of FA Components Molecular Switches in FA Future Challenges	
Protein Interaction Mapping by Coprecipitation and Mass Spectrometric		References	
Identification Shao-En Ong and Matthias Mann	295	CHAPTER 177 WASp/Scar/WAVE Charles L. Saxe	323
Introduction General Considerations of the Coprecipitation Experin GST-Tagged Proteins Antibodies Epitope Tags	nent	Introduction WASp Scar/WAVE References	
Mass Spectrometric Approaches Outlook References		CHAPTER 178 Synaptic NMDA-Receptor Signaling Complex	329
Chapter 173		Mary B. Kennedy	
Proteomics, Fluorescence, and	201	Introduction	
Binding Affinity Paul R. Graves and Timothy A. J. Haystead Introduction	301	Structure of the NMDA Receptor Signaling Complex Orchestration of Responses to Ca ²⁺ Entering through the NMDA Receptor	

Chapter 179		Major Regulatory Mechanisms that Control Specificity	' in
Toll Family Receptors	333	S. cerevisai MAPK Cascades References	
Hana Bilak, Servane Tauszig-Delamasure, and Jean-Luc Im-	ller	References	
Introduction		CHAPTER 184	
Structure Function of Toll Receptors		X ^{c,v} Mammalian MAP Kinases	365
Signaling by Toll Family Receptors		Roger J. Davis	
References		Introduction	
<u>Chapter 180</u>		The ERK Group of MAP Kinases	
Signaling and the Immunological		The p38 Group of MAP Kinases	
Synapse	339	The JNK Group of MAP Kinases	
Andrey S. Shaw		MAP Kinase-Related Protein Kinases	
Introduction		MAP Kinase Docking Interactions Scaffold Proteins	
Brief Introduction to T Cell Biology		References	
Initiation of TCR Signaling			
Definition of the Immunological Synapse		CHAPTER 185	
Immunological Synapses and T-Cell Development Synapses and Different Kinds of T Cells		Subcellular Targeting of PKA through	
Natural Killer Cell Synapses		AKAPs: Conserved Anchoring and	
The Function of the Immunological Synapse		Unique Targeting Domains	377
Immunological Synapses and TCR Downregulation		Mark L. Dell'Acqua	
Conclusion References		Introduction	
References		Structurally Conserved PKA Anchoring Determinants	
<u>Chapter 181</u>		Unique Subcellular Targeting Domains	
The Ubiquitin-Proteasome System	347	Probing Cellular Functions of AKAP-PKA Anchoring	
Mark Hochstrasser		Conclusions and Future Directions	
Introduction		References	
Overview of the Ubiquitin-Proteasome System			
Components of the Ubiquitin Ligation and		<u>Chapter 186</u>	
Deubiquitination Pathways The 20S and 26S Proteasomes		AKAP Signaling Complexes: The	
Degradation Signals or Degrons		Combinatorial Assembly of Signal	
Examples of Regulation of Protein Ubiquitination		Transduction Units	383
References		John D. Scott and Lorene K. Langeberg	
CHAPTER 182		Introduction	.*
Caspases: Cell Signaling by Proteolysis	351	G-Protein Signaling Through AKAP Signaling	
Guy S. Salvesen	001	Complexes Kinase/Phosphatase Signaling Complexes	
Protease Signaling		CAMP Signaling Units	
Apoptosis and Limited Proteolysis		Conclusions and Perspectives	
Caspase Activation		References	
Regulation by Inhibitors		Cuapan 197	
IAP Antagonists References		CHAPTER 187	200
References		Protein Kinase C-Protein Interaction Peter J. Parker, Joanne Durgan, Xavier Iturrioz, and	389
Chapter 183		Sipeki Szabolcs	
MAP Kinase in Yeast	357	Introduction	
Elaine A. Elion		Priming	
Introduction		Activation	
Yeast Cells Use Multiple MAPKs to Respond to a		Substrates and Pathways	
Wide Variety of Stimuli Functionally Defining S. cerevisiae MAPK		PKC Inactivation Perspectives	
Cascades		References	

The Gene Families

Implications of Multiple Gene Families/Splice Variants

PDE Inhibitors as Therapeutic Agents

Dendrite Protein Phosphatase Complexes Roger J. Colbran	397	C	
Introduction The Importance of Dendritic Localization Protein Phosphatase 1 Calcineurin (Protein Phosphatase 2B) Dendritic Phosphatase Substrates Role of Phosphatases in Synaptic Plasticity Summary		CHAPTER 193 The cAMP-Specific Phosphodiesterases: A Class of Diverse Enzymes That Defines the Properties and Compartmentalization of the cAMP Signal Marco Conti	437
References		Structure of the cAMP-PDEs: Catalytic and Regulator Domains	У
CHAPTER 189 Protein Phosphatase 2A Adam M. Silverstein, Anthony J. Davis, Vincent A. Bielinski Edward D. Esplin, Nadir A. Mahmood, and Marc C. Mumby		Subcellular Targeting of the cAMP-PDEs and cAMP Signal Compartmentalization Regulation of cAMP-PDEs References	
Introduction PP2A Regulatory Subunits Mediate Proximity Interactions PP2A-Interacting Proteins References		CHAPTER 194 cAMP/cGMP Dual-Specificity Phosphodiesterases Marie C. Weston, Lena Stenson-Holst, Eva Degerman, and Vincent C. Manganiello	441
Section F: Cyclic Nucleotides Jackie Corbin, Editor		Introduction PDE1 (Ca ²⁺ /Calmodulin-dependenet PDE) PDE2 (cGMP-stimulated PDE) PDE3 (cGMP-inhibited cAMP PDE)	
<u>Chapter 190</u>		PDE10	
Adenylyl Cyclases Matt Whorton and Roger K. Sunahara	419	PDE11 Conclusions References	
Introduction Structure-Function Regulation Physiology Summary References		CHAPTER 195 Phosphodiesterase-5 Sharron H. Francis and Jackie D. Corbin Introduction	447
CHAPTER 191 Guanylyl Cyclases Ted D. Chrisman and David L. Garbers	427	Gene Organization and Regulation of Expression General Structure Concluding Remarks References	
Historic Perspectives Guanylyl Cyclases Guanylyl Cyclase Ligands eGMP Effectors Guanylyl Cyclases and Cell Growth Regulation References		CHAPTER 196 Structure, Function, and Regulation of Photoreceptor Phosphodiesterase (PDE6) Rick H. Cote	453
CHAPTER 192 Phosphodiesterase Families Jennifer L. Glick and Joseph A. Beavo	431	Introduction Structure and Subcellular Localization of Rod PDE6 Regulation of Rod PDE6 Catalysis by γ Catalytic Properties of Nonactivated and	
Introduction		Activated PDE6P	

Where Do We Go from Here?

Roles of the GAF Domains in PDE6 Regulation

Conclusion

CHAPTER 197 Spatial and Temporal Relationships of Cyclic Nucleotides in Intact Cells Manuela Zaccolo, Marco Mongillo, and Tullio Pozzan	459	CHAPTER 202 Peptide Substrates of Cyclic Nucleotide- Dependent Protein Kinases Ross I. Brinkworth, Bostjan Kobe, and Bruce E. Kemp	495
The Complexity of Cyclic Nucleotides Signaling Methodological Advances Functional Compartments of cAMP in Heart Cells Spatio-temporal Aspects of Cyclic Nucleotides Signaling in Neurons Conclusions References		Introduction Peptide Substrate Recognition Comparison of Kinase Substrate Acceptor Loci Optimum Recognition Sequences Comparison of PKA and PKG Specificity Conclusions References	
CHAPTER 198 Regulation of Cyclic Nucleotide Levels by Sequestration Jackie D. Corbin, Jun Kotera, Venkatesh K. Gopal, Rick H. Cote, and Sharron H. Francis	465	CHAPTER 203 Physiological Substrates of PKA and PKG Kjetil Tasken, Anja Ruppelt, John Shabb, and Cathrine R. Carlson	501
Introduction Sequestration of cGMP in Rod Photoreceptor Cells by PDE6 Sequestration of cGMP by PDE5 References		Introduction Abundance of PKA and PKG Phosphorylation Sites in the Human Proteome Physiological Substrates Concluding Remarks References	
CHAPTER 199 cAMP-Dependent Protein Kinase Susan S. Taylor and Elzbieta Radzio-Andzelm Introduction Catalytic Subunit Protein Kinase Inhibitor Regulatory Subunits References	471	CHAPTER 204 Effects of cGMP-Dependent Protein Kinase Knockouts Franz Hofmann, Robert Feil, Thomas Kleppisch, and Claudia Werner Cyclic GMP-Dependent Protein Kinases: Genes and Knockouts Outlook	511
CHAPTER 200 Cyclic GMP-Dependent Protein Kinase Thomas M. Lincoln Introduction Biochemical and Molecular Biology of PKG Isoforms Physiologic Roles of PKG Concluding Remarks References	479	CHAPTER 205 Cyclic Nucleotide-Regulated Cation Channels Martin Bie: and Andrea Gerstner Introduction General Features of Cyclic Nucleotide-Regulated Cation Channels CNG Channels	515
CHAPTER 201 Inhibitors of Cyclic Nucleotide-Dependent Protein Kinases Wolfgang R. G. Dostmann	487	HCN Channels References CHAPTER 206	
Introduction Cyclic Nucleotide Binding Site-Targeted Inhibitors ATP Binding Site-Targeted Inhibitors Peptide Binding in Site-Targeted Inhibitors		Epacs, cAMP-Binding Guanine Nucleotide Exchange Factors for Rap1 and Rap2 Holger Rehman, Johan de Rooij, and Johannes L. Bos	521
Conclusions References		Introduction The Epac Family	

The cAMP-Binding Domain of Epac Closely Resembles Those of PKA and Channels Epac Is Conserved Through Evolution Properties of Epac Expression and Subcellular Localization of Epacs	CHAPTER 211 Cyclic Nucleotide Specificity and Cross-Activation of Cyclic Nucleotide Receptors 545 Clay E. S. Comstock and John B. Shabb
Cellular Function of Epacs References CHAPTER 207 Cyclic Nucleotide-Binding Phosphodiesterase and Cyclase GAF Domains 525	cAMP Cross-Activation of PKG cGMP Cross-Activation of PKA Molecular Basis for cAMP/cGMP Selectivity of PKA and PKG Other Cyclic Nucleotide Receptors References
Sergio E. Martinez, Xiao-Bo Tang, Stewart Turley, Wim G. J. Hol, and Joseph A. Beavo Introduction Atomic Structure References	CHAPTER 212 Cyclic Nucleotide Analogs as Tools to Investigate Cyclic Nucleotide Signaling Anne Elisabeth Christensen and Stein Ove Døskeland 549
CHAPTER 208 cAMP Signaling in Bacteria J. M. Passner 531	Introduction Use of cNMP Analogs: Guidelines and Examples Chemistry and Properties of Cyclic Nucleotide Analogs Future Developments References
Introduction and Significance Background and History Transcriptional Regulation by CAP CAP Permits Differential Gene Regulation at Different cAMP Concentrations A Second cAMP-Binding Site in a CAP Monomer Perspectives and Conclusions References	Section G: G Proteins Heidi Hamm, Editor CHAPTER 213 Signal Transduction by G Proteins — Basic Principles, Molecular Diversity, and Structural Basis of Their Actions Lutz Birnbaumer 557
CHAPTER 209 Cyclic Nucleotide Signaling in Paramecium Jürgen U. Linder and Joachim E. Schultz Introduction 535	Introduction Ras, the Prototypic Regulatory GTPases Heterotrimeric G Proteins Mechanism of G-Protein Activation by Receptors and Modulation of Activity References
cAMP Formation and Adenylyl Cyclase Guanylyl Cyclase and cGMP Formation Downstream of Cyclic Nucleotide Formation References	CHAPTER 214 Genetic Analysis of Heterotrimeric G-Protein Function Juergen A. Knoblich 571
CHAPTER 210 Cyclic Nucleotide Signaling in Trypanosomatids Roya Zoraghi and Thomas Seebeck 539	Introduction Signaling by Heterotrimeric G Proteins in Yeast Heterotrimeric G-Protein Function in <i>Drosophila</i> Conclusions References
Introduction Cyclic Nucleotide Signaling, Cell Proliferation, and Differentiation Individual Components of the Cyclic Nucleotide Signaling Pathways Cyclic Nucleotides and Host Parasite Intervention	CHAPTER 215 Heterotrimeric G Protein Signaling at Atomic Resolution 575 David G. Lambright
Concluding Remarks References	Introduction Architecture and Switching Mechanism of the G_{α} Subunits

Insight into the GTP Hydrolytic Mechanism from an Unexpected Transition State Mimic $G_{\beta\gamma}$ with and without \dot{G}_{α} Phosducin and $G_{\alpha\gamma}$ $G_{S\alpha}$ and Adenylyl Cyclase		Regulators of G_z Signaling: RGS Proteins Effectors of G_z Signaling $G\alpha_z$ Knockout Mice Summary References	
Filling in the GAP Visual Fidelity What Structures May Follow References		CHAPTER 220 Effectors of G_{00} Signaling Prahlad T. Ram, J. Dedrick Jordan, and Ravi Iyengar	605
CHAPTER 216 In Vivo Functions of Heterotrimeric G Proteins	581	Introduction Conclusions References	
Stefan Offermanns Introduction Development		CHAPTER 221 Phosphorylation of G Proteins Louis M. Luttrell and Deirdre K. Luttrell	609
Central Nervous System Immune System Heart Sensory Systems Hemostasis Conclusions		Introduction Serine Phosphorylation Tyrosine Phosphorylation Conclusions References	
References CHAPTER 217 Regulation of G Proteins by Covalent Modification	585	CHAPTER 222 Mono-ADP-Ribosylation of Heterotrimeric G Proteins Maria Di Girolamo and Daniela Corda	613
Jessica E. Smotrys and Maurine E. Linder Introduction N-Terminal Acylation of G_{α} C-Terminal Modification of G_{γ} Conclusions		Introduction The Mono-ADP-Ribosylation Reaction Bacterial Toxin-Induced ADP-Ribosylation Endogenous Mono-ADP-Ribosylation References	
CHAPTER 218 G-Protein-Coupled Receptors, Cell	500	CHAPTER 223 Using Receptor-G-Protein Chimeras to Screen for Drugs	619
Transformation, and Signal Fidelity Hans Rosenfeldt, Maria Julia Marinissen, and J. Silvio Gutk	589 aind	Graeme Milligan, Richard J. Ward, Gui-Jie Feng, Juan J. Carrillo, and Alison J. McLean	
Introduction Heptahelical Receptors and Tumorigenesis G-Protein Signaling in Cancer A Matrix of MAPK Cassettes Links GPCRs to Biological Outcomes G-Protein-Independent Signaling	.,	Receptor-G-Protein Chimeras: An Introduction Defining the Signal Guanine Nucleotide Exchange Assays Constitutive Activity and Inverse Agonism Conclusions References	
GPCR Effectors Are Organized by Scaffolding Molec Conclusion: GPCR Biology Requires Both Signal Integration and Separation References	ules	CHAPTER 224 Specificity of G Protein βγ Dimer Signaling Janet D. Robishaw, William F. Schwindinger, and	623
CHAPTER 219 Signaling through G _z Jingwei Meng and Patrick J. Casey	601	Carl A. Hansen Introduction	
General Properties Receptors That Couple to G _z		Diversity of the β and γ Gene Families Assembly of the βγ Dimer Specificy of G Protein βγ Dimer Signaling	

Conclusion References		CHAPTER 230 Regulation of Synaptic Fusion by	
CHAPTER 225		Heterotrimeric G Proteins	663
The RGS Protein Superfamily David P. Siderovski and T. Kendall Harden	631	Simon Alford and Trillium Blackmer Introduction	
Introduction The Signature RGS-Box as a Gα GAP Gα GAP and Other Signaling Regulatory Activities of RGS Family Members	•	The Vesicle Fusion Machinery G Protein-Coupled Receptor Mediated Modulation at the Presynaptic Terminal Possible Mechanisms of Presynaptic Inhibition by	
References		G Proteins Presynaptic Ca ²⁺ Stores and Modulation of	
CHAPTER 226 Mechanism of βγ Effector Interaction Tohru Kozasa	639	Neurotransmitter Release G Proteins and Phosphorylation References	
Introduction Effectors Interacting with βγ Subunits Specificity of the Interaction between βγ Subunit and Effectors		CHAPTER 231 G Protein Regulation of Channels Wiser Ofer and Lily Yeh Jan	667
References		Interaction with K+ Channels The GBy Interacting Domain of GIRK	
CHAPTER 227 βγ Signaling in Chemotaxis Carol L. Manahan and Peter N. Devreotes	645	Coupling of GIRK Activation to Specific Receptors Calcium Channel Interaction with G Proteins	
Introduction Evidence that G Proteins Are Involved in Chemotaxis PI3Ks — Role in Chemotaxis? Lipid Phosphatases, PTEN and SHIP References		G Protein Interacting Domains The Gβγ Interacting Domain of HVA Ca ^{2±} Channels Modulation of Gβγ Inhibition Voltage-Independent G-Protein-Mediated Inhibition of Calcium Channels References	·
CHAPTER 228 Reversible Palmitoylation in G-Protein Signaling Philip Wedegaertner	651	CHAPTER 232 Ras and Cancer Frank McCormick	671
Introduction Sites of Palmitoylation in G_{α} and RGS Proteins Activation-Regulated Palmitoylation of G_{α} Mechanisms of Reversible Palmitoylation Functions of Reversible Palmitoylation		Introduction: Ras Activation in Cancer Pathways Downstream of Ras Mouse Models of Cancer Prospects for Cancer Therapy Based on Ras References	
Conclusion References		CHAPTER 233	
CHAPTER 229 G Proteins Mediating Taste Transduction	657	The Influence of Cellular Location on Ras Function Janice E. Buss, Michelle A. Booden, and John T. Stickney	675
Sami Damak and Robert F. Margolskee		Cytosolic Ras Is not Functional	
Introduction α-Gustducin α-Transducin Other G Protein α Subunits		After Modifications by Endomembrane Enzymes, Ras Proteins Move Toward the Cell Surface Destination-Cell Surface: Ras Proteins Distribute Amo Several Plasma Membrane Domains	
βγ Subunits G-Protein-Coupled Receptors		Ras Proteins Finally Become Active at the Plasma Membrane	
Second Messenger Pathways Conclusion References		Endocytosis — A New Stage for Ras Signaling Drugs that Affect Ras Membrane Binding References	

Chapter 234		CHAPTER 238	
Role of R-Ras in Cell Growth	681	Regulation of the NADPH Oxidase by	
Gretchen A. Murphy, Adrienne D. Cox, and Channing J. Der		Rac GTPase Becky A. Diebold and Gary M. Bokoch	705
Introduction		Components and Regulation of the NADPH Oxidase	
General Properties of R-Ras Proteins:		The Role of Rac in NADPH Oxidase Regulation	
Variations on Ras		Current Models of Rac Function in NADPH Oxidase	
R-Ras		Regulation	
TC21/R-Ras-2		Rac GTPase—A More General Role in Regulating	
M-Ras/R-Ras-3		Oxidant-Bases Signaling?	
Conclusions References		References	
References		Chapter 239	
Chapter 235		The Role of Rac and Rho in Cell	
		Cycle Progression	711
Molecular and Structural		Laura J. Taylor and Dafna Bar-Sagi	, 11
Organization of Rab GTPase Trafficking	600		
Networks	689	Introduction	
Christelle Alory and William E. Balch		Regulation of G1 Progression	
Introduction		The Function of Rac and Rho in Cell Cycle	
Rab Proteins are Recycling GTPases		Progression and Transformation	
Rab Proteins: An Evolutionary Conserved Family		Cell Cycle Targets of Rac and Rho	
Structural Organization of the Rab Proteins		Future Perspectives References	
Posttranslational Modification and Localization		References	
Effector Molecules: REP/CHM, GEF, Effectors		Chapter 240	
(Motors/Tethers/Fusogens), GAP, and GDI		Cdc42 and Its Cellular Functions	715
Rab Dysfunction and Disease		Wannian Yang and Richard A. Cerione	, 10
Perpective			
References		Introduction	
		Biological Effects of Cdc42	
Chapter 236		Cell Adhesion and Migration	
Cellular Roles of the Ran GTPase	695	Cell Polarity Molecular Mechanisms Underlying the Biological	
Jomon Joseph and Mary Dasso		Activities of Cdc42	
Introduction		Conclusions	
Introduction to the Ran Pathway		References	
Structural Analysis of Ran Pathway Components		CHAPTER 241	
Ran's Role in Nuclear Transport		CHAPTER 241	
Ran's Function in Mitotic Progression		Tissue Transglutaminase: A Unique	
Ran's Function in Spindle Assembly		GTP-Binding/GTPase	721
Ran's Role in Postmitotic Nuclear Assembly		Richard A. Cerione	
Conclusions		Introduction	
References		TGase as a GTP-Binding/GTPase	
		New Links to Biological Function	
Chapter 237		Future Directions	
Rho Proteins and Their Effects on		References	
the Actin Cytoskeleton	701	Chapter 242	
Anja Schmidt and Alan Hall			
Introduction		The Role of ARF in Vesicular	=
Effects of Rho GTPases on the Actin Cytoskeleton		Membrane Traffic	727
Signaling from Rho GTPases to the Actin		Melissa M. McKay and Richard A. Kahn	
Cytoskeleton		The ARF Family of Regulatory GTPases	
Conclusions		ARF as a Regulator of Membrane Traffic	
References		References	

The G Domain Functional Unit Guanine Nucleotide Exchange Factors

CHAPTER 243 Yeast Small G Protein Function: Molecular Basis of Cell Polarity in Yeast 733	Effector B Via Switches and Others Conclusions References
Hay-Oak Park and Keith G. Kozminski Introduction Conclusion References	CHAPTER 248 Conventional and Unconventional Aspects of Dynamin GTPases Sandra L. Schmid 76.
CHAPTER 244 Farnesyltransferase Inhibitors 737 James J. Fiordalisi and Adrienne D. Cox Introduction Farnesylation and Protein Function Ras—The Prototype of Farnesylated Proteins Indentification and Development of FTIs FTI Activity in Cell Culture and Animal Models Alternative Prenylation in the Presence of FTIs FTIs as Pharmacological Tools to Study Signaling and Biology Targets of FTIs Inhibition of Signaling by FTIs Summary of Prospects	Introduction Common and Unique Features of Dynamin as a GTPase Dynamin's Function in Endocytic Vesicle Formation Dynamin's Siblings: The Dynamin Subfamily of GTPases Dynamin as a Signaling Molecule Conclusion and Perspectives References CHAPTER 249 Mx Proteins: High Molecular Weight GTPases with Antiviral Activity George Kochs, Othmar G. Engelhardt, and Otto Haller Antiviral Activity of Mx GTPases Mx Proteins Belong to the Superfamily of High
References CHAPTER 245 Structure of Rho Family Targets Helen R. Mott and Darerca Owen CRIB Proteins	Molecular Weight GTPases Cellular Interaction Partners of Mx GTPases References Section H: Developmental Signaling Geraldine Weinmaster, Editor
Non-CRIB Rac Effectors Rho Effectors Concluding Remarks References CHAPTER 246 Standard Footspace of Physics 751	CHAPTER 250 Toll-Dorsal Signaling in Dorsal-Ventral Patterning and Innate Immunity Ananya Bhattacharya and Ruth Steward 779
Jason T. Snyder, Kent L. Rossman, David K. Worthylake, and John Sondek Introduction Structural Accomplishments DH Domain Features DH-Associated PH Domains PH Domain Configurations Mechanisms of Nucleotide Exchange Molecular Recognition of Rho GTPase Substrates External Regulation of the DH and PH Domains References	The Toll-Dorsal Pathway Maturation of the Toll Ligand Toll Signaling Establishes the Embryonic Dorsal Gradient Dorsal Regulates the Function of Zygotic Genes The Intracellular Pathway Is Conserved in the Drosophila Immune Response Nuclear Import of Rel Proteins References CHAPTER 251 Developmental Signaling: JNK Pathway
CHAPTER 247 Structural Considerations of Small GTP-Binding Proteins Alfred Wittinghofer Introduction 757	in Drosophila Morphogenesis Beth E. Stronach and Norbert Perrimon Introduction The Paradigm of JNK Signaling: Dorsal Closure Thorax Closure Follicle Cell Morphogenesis

A New Paradigm: Planar Cell Polarity

Cellular Stress Response and Wound Healing

Perspectives		CHAPTER 257	-
References		Notch Signaling in Vertebrate	
Chapter 252		Development	813
Wnt Signaling in Development Christian Wehrle, Heiko Lickert, and Rolf Kemler	789	Chris Kintner Introduction	
Introduction Wnt Signaling in Invertebrate Development Wnt Signaling in Vertebrate Development Wnt/β-Catenin Target Genes		Components Mediating Vertebrate Notch Signaling Notch Signaling in Vertebrate Development Summary References	
References		CHAPTER 258	
CHAPTER 253 Hedgehog Signaling and Embryonic Development Mark Merchant, Weilan Ye, and Frederic de Sauvage	793	Reiterative and Concurrent Use of EGFR and Notch Signaling during <i>Drosophila</i> Eye Development Raghavendra Nagaraj and Utpal Banerjee	827
The Hedgehog Proteins: Generation and Distribution Transmitting the Hh Signal Hh in Development and Disease References		Introduction Establishment of the Eye Primordium Proliferation and D/V Patterning Morphogenetic Furrow and R8 Specification R-Cell Specification	
CHAPTER 254		Sequential Linkage between Notch and EGFR	
Control of Left-Right (L/R) Determination in Vertebrates by the Hedgehog Signaling	799	Pathways Parallel Linkage between EGFR and Notch Pigment Cell Differentiation and Apoptosis Conclusion References	
Introduction		C	
The Discovery of the First Molecular Asymmetries in Vertebrate Embryos and the Role of SHH The Role of a Composite HH Signal during L/R		CHAPTER 259 BMPs in Development Karen M. Lyons and Emmanuele Delot	833
Determination in the Mouse			
References		Introduction Gradients of BMP Activity	
Chapter 255		Establishing BMP Ligand Gradients	
EGF-Receptor Signaling in Caenorhabditis elegans Vulval Development Nadeem Moghal and Paul W. Sternberg	805	Extracellular Modifiers of BMP Activity Interpreting the Gradient-Role of BMP Receptors Differential Gene Activity in Response to BMP	
The Core LET-23 Signaling Pathway Tissue Specificity		Signal Transduction Intracellular Negative Regulation of BMP Signaling	
Positive and Negative Regulators Prospects References		Lessons from Loss-of-Function Studies in Mammals Conclusions	
Cara proper 256		References	
CHAPTER 256		CHAPTER 260	
Induction and Lateral Specification Mediated by LIN-12/Notch Proteins Sophie Jarriault and Iva Greenwald	809	Neurotrophin Signaling in Development Albert H. Kim and Moses V. Chao	839
The LIN-12/Notch Pathway Cell-Cell Interactions Mediated by the LIN-12/Notch Pathway The Role of LIN-12/Notch Proteins: Suppression of Differentiation versus Specification of Binary Cell Fate Decisions References		Introduction The Neurotrophin Ligands Neurotrophin Receptors Signaling Specificity during Development The Importance of Tetrograde Transport Interacting Proteins References	

Andrew W. Stoker

CHAPTER 261 PDGF Receptor Signaling in Mouse Development Richard A. Klinghoffer	845	Introduction RPTPs and the Visual System Neuromuscular System Further Axon Growth and Guidance Roles Axonal Signaling by RPTPs	
Introduction PDGTβR Signaling In Vivo PDGFαR Signaling In Vivo Specificity of PDGFR Signaling In Vivo References CHAPTER 262		CHAPTER 266 Attractive and Repulsive Signaling in Nerve Growth Cone Navigation Guo-li Ming and Mu-ming Poo	871
VEGF and the Angiopoietins Activate Numerous Signaling Pathways that Govern Angiogenesis Christopher Daly and Jocelyn Holash Introduction Endothelial Cell Proliferation VEGF Promotes Vascular Permeability Ang-1 Inhibits Vascular Permeability Vessel Destabilization and EC Migration Regulation of EC Survival during Angiogenesis	849	Introduction Netrin Signaling Semaphorin Signaling Slit Signaling Ephrin Signaling Nogo and Myelin-Associated Clycoprotein Signaling Critical Roles of Modulatory Signals Concluding Remarks References	
Conclusion References CHAPTER 263 Vascular Endothelial Growth Factors and their Receptors in Vasculogenesis, Angiogenesis, and Lymphangiogenesis Marja K. Lohela and Kari Alitalo Vasculogenesis, Angiogenesis, and Lymphangiogenesis The Vascular Endothelial Growth Factors and their Rece VEGF and VEGFR-1 and -2 are Essential for	855 is eptors	CHAPTER 267 Semaphorins and their Receptors in Vertebrates and Invertebrates Eric F. Schmidt, Hideaki Togashi, and Stephen M. Strittmatter The Semaphorin Family Receptors for Semaphorins Intracellular Signaling Pathways Summary and Future Directions References	877
Vasculogenesis and Angiogenesis Lymphangiogenesis is Regulated by VEGFR-3 and its Ligands VEGF-C and -D Concluding Remarks References	S	CHAPTER 268 Signaling Pathways that Regulate Neurons Specification in the Spinal Cord Ann E. Leonard and Samuel L. Pfaff	al 883
CHAPTER 264 Signaling from FGF Receptors in Development and Disease Monica Kong and Daniel J. Donoghue	861	Patterning along the Dorsoventral Axis Dorsal Spinal Cord Development Ventral Spinal Cord Development Rostrocaudal Specification References	
Introduction Expression of FGFR during Development Role of FGFR in Development Syndromes Associated with FGFRs Signaling Pathways Mediated by FGFRs Summary		CHAPTER 269 Cadherins: Interactions and Regulation of Adhesivity Barbara Ranscht	889
References CHAPTER 265 The Role of Receptor Protein Tyrosine Phosphatases in Axonal Pathfinding	867	Introduction The Members of the Family Multiple Modes for Regulating Cadherin Adhesive Activity Conclusions and Perspectives	

VOLUME 3

Contributors

xlv

PART III

NUCLEAR AND CYTOPLASMIC EVENTS: TRANSCRIPTIONAL AND POST-TRANSCRIPTIONAL REGULATION

Michael Karin, Editor

PART III

Introduction

Michael Karin

Section A: Nuclear Receptors

Michael G. Rosenfeld, Editor

CHAPTER 270

History of Nuclear Receptors

Elwood V. Jensen

Introduction

Discovery of Receptors and Shift in Research Direction Receptor Forms and Physiological Action Subsequent Discoveries Relevant to Receptor Structure and Function

References

CHAPTER 271

Regulation of Basal Transcription by RNA Polymerase II

Sohail Malik and Robert G. Roeder

Introduction

The Preinitiation Complex

Global Mechanisms of PIC Function

Gene-Specific Regulation of PIC Function by

Transcriptional Activators

Conclusion

References

CHAPTER 272

Structural Mechanisms of Ligand-Mediated Signaling by Nuclear Receptors 21

H. Eric Xu and Millard H. Lambert

Introduction

Overall Structure of the LBD

Ligand-Binding Pockets

Ligand-Mediated Activation: Mouse Trap versus

Charged Clamp

Ligand-Mediated Repression

Dimerization

Summary References

<u>CHAPTER 273</u> Nuclear Receptor Coactivators

25

Riki Kurokawa and Christopher K. Glass

Introduction

Mechanism of Coactivator Recruitment

General Classes of Coactivator Complexes

Coactivators as Targets of Signal Transduction Pathways

Conclusion

References

CHAPTER 274

Corepressors in Mediating Repression by

Nuclear Receptors

29

35

Kristen Jepsen and Michael G. Rosenfeld

Introduction

N-CoR and SMRT in Repression by Nuclear Receptors

Purification of Corepressor Complexes

Other Nuclear Receptor and Transcription Factor Partners

of N-CoR/SMRT

Multiple Mechanisms of N-CoR/SMRT Regulation

Roles in Development and Disease

Other Mediators of Nuclear Receptor Repression

Conclusion

7

11

References

CHAPTER 275

Steroid Hormone Receptor Signaling

Vincent Giguère

Introduction

Activation by the Hormone

Hormone-Independent Activation

Cross-Talk with Other Transcription Factors

Nongenomic Action of Steroid Hormones

Estrogen Related Receptors

Selective Steroid Hormone Receptor Modulators

References

CHAPTER 276

PPARγ Signaling in Adipose Tissue

Development

39

Robert Walczak and Peter Tontonoz

Introduction

PPARy: A Dominant Regulator of Adipose Tissue

Development

Analysis of PPARy Function in Animal Models

Transcriptional Networks in Adipose Tissue Development

Negative Regulation of Adipocyte Differentiation

PPARγ, TNF-α Signaling Antagonism and Insulin Resistance

PPARy and Cell Cycle Regulation

CHAPTER 277		The Neuronal Connection	
Orphan Nuclear Receptors Barry Marc Forman	47	References	
Classical Receptors versus Orphan Receptors Orphan Receptors and Metabolite-Derived Signals Orphan Receptors and Xenobiotic Signals Future Directions		Section B: Transcription Factors Marc Montiminy, Editor	
References		Chapter 282	
CHAPTER 278		JAK-STAT Signaling Christian W. Schindler	77
Identification of Ligands for Orphan		Introduction	
Nuclear Receptors Steven A. Kliewer and Timothy M. Willson	53	The JAK-STAT Paradigm The JAK Family	
Introduction		The STAT Family	
PPARs: Fatty Acid Sensors		A Promising Future	
LXRs: Cholesterol Sensors		References	
FXR: Bile Acid Sensor		Chapter 283	
PXR and CAR: Xenobiotic Sensors Ligands for Other Orphan Nuclear Receptors		FOXO Transcription Factors: Key	
Conclusion		Targets of the PI3K-Akt Pathway That	
References		Regulate Cell Proliferation, Survival, and	
CHAPTER 279		Organismal Aging	83
Orphan Receptor COUP-TFII and		Anne Brunet, Hien Tran, and Michael E. Greenberg	
Vascular Development	57	Introduction FOVO S. 1.6. III. 6	
Fabrice G. Petit, Sophia Y. Tsai, and Ming-Jer Tsai		Identification of the FOXO Subfamily of Transcription Factors	
Introduction		Regulation of FOXO Transcription Factors by the	
Vascular Development		PI3K-Akt Pathway	
PPARγ: Inhibitor of Angiogenesis COUP-TFII: Positive Effector in Angiogenesis		Other Regulatory Phosphorylation Sites in FOXOs Mechanism of the Exclusion of FOXOs from the	
Conclusion		Nucleus in Response to Growth Factor Stimulation	
References		Transcriptional Activator Properties of FOXOs	
CHAPTED 280		FOXOs and the Regulation of Apoptosis FOXOs Are Key Regulators of Several Phases of	
<u>CHAPTER 280</u> Crosss-Talk between Nuclear Receptors		the Cell Cycle	
and Other Transcription Factors	61	FOXOs in Cancer Development: Potential Tumor	
Peter Herrlich	V.	Suppressors Role of FOXOs in the Response to Stress and	
Introduction		Organismal Aging	
Proliferation and Proinflammatory Pathways		FOXOs and the Regulation of Metabolism in	
Nuclear Receptors Induced Expression of Inhibitory Molecules		Relation to Organismal Aging Conclusion	
Immediate Hormone Responses		References	
Direct Modulation of Transcription Factors		G	
Conclusion References		Chapter 284	
References		Multiple Signaling Routes to Histone	0.4
CHAPTER 281		Phosphorylation Claudia Crosio and Paolo Sassone-Corsi	91
Drosophila Nuclear Receptors	69		
Kirst King-Jones and Carl S. Thummel		Introduction Histone Phosphorylation and Gene Activation	
Introduction		Histone Phosphorylation and DNA Repair	
Nuclear Receptors and Embryonic Pattern Formation Ecdysone Regulatory Hierarchies		Histone Phosphorylation and Apoptosis	
Ladysonic Regulatory Interacentes		Histone Phosphorylation and Mitosis	

			
Conclusions References		Coordinate Regulation of Nuclear Import and Export: Calcium-Dependent Nuclear Localization of NFAT	
Chapter 285		Transcription Factors Regulated Nuclear Transport of Non-DNA-Binding	
Multigene Family of Transcription		Transcriptional Regulatory Proteins	•
Factor AP-1	99	Conclusion	•
Peter Angel		References	
Introduction		<u>Chapter 290</u>	
General Structure of AP-1 Subunits		Proteasome/Ubiquitination	129
Transcriptional and Posttranslational Control of		Daniel Kornitzer and Aaron Ciechanover	
AP-1 Activity		Protein Degradation and the Ubiquitin/Proteasome Sy	stem
Function of Mammalian AP-1 Subunits: Lessons from Loss-of-Function Approaches in Mice		Regulation of Ubiquitination by Substrate Modification	
References		Regulation of Ubiquitin Ligase Activity	
Keleryhee		Protein Processing by the Ubiquitin System	
CHAPTER 286		Modulation of Kinase Activity by Ubiquitination	
NFκB: A Key Integrator of Cell		Conclusion	
Signaling	107	References	
John K. Westwick, Klaus Schwamborn, and Frank Mercurio		Chapter 291	
		Fluorescence Resonance Energy Transfer	
References		Microscopy and Nuclear Signaling	135
CHAPTER 287		Ty C. Voss and Richard N. Day	133
Transcriptional Regulation via the cAMP		·	
Responsive Activator CREB	115	Introduction	
Marc Montminy and Keyong Du	113	References	
		Chapter 292	
The Transcriptional Response to cAMP		The Mammalian Circadian	
Mechanism of Transcriptional Activation via CREB		Timing System	139
Signal Discrimination via CREB		Ueli Schibler, Steven A. Brown, and Jürgen A. Ripperger	137
Secondary Phosphorylation of CREB: Ser142			
Methylation of the KIX Domain		Introduction	
Cooperative Binding with MLL		The Molecular Oscillator	
References		Photic Entrainment of the Central Pacemaker Outputs of the SCN Pacemaker	
~ ***		Outputs via Subsidiary Clocks	
Chapter 288		Conclusions and Perspectives	
The NFAT Family: Structure,		References	
Regulation, and Biological Functions	119	G 402	
Pernando Macian and Anjana Rao		<u>Chapter 293</u>	
Introduction		Protein Arginine Methylation	145
Structure and DNA-Binding		Michael David	
Regulation		Introduction	
Transcriptional Functions		Arginine Methylation and Arginine-Methyltransferase	es
Biological Programs Regulated by NFAT		Function of Arginine Methylation	
Perspectives References		Role of Arginine Methylation in Signal Transduction	
References		References	
CHAPTER 289		CHAPTER 294	
Transcriptional Control through		Transcriptional Activity of Notch and	
Regulated Nuclear Transport	125	CSL Proteins	149
Steffan N. Ho		Elise Lamar and Chris Kintner	177
•			
Introduction Regulated Nuclear Transport: Overview		Introduction Components of the Notch Transcriptional Complex	
-industrial resistant resimborn of the trott		Component of the free Runderphona Complex	

Notch Transcriptional Activity In Vivo Conclusion References CHAPTER 295 The β-Catenin: LEF/TCF Signaling Complex: Bigger and Busier than Before Reiko Landry and Katherine A. Jones Introduction Regulated Proteolytic Turnover of β-Cat Regulation of the Wnt-Assembled Enhancer Complex	161	SOS Response LexA Cleavage and Other Self-Cleavage Reactions Regulating the SOS Response Structures of Y-Family Polymerases Conclusions References CHAPTER 300 Oxidative Stress and Free Radical Signal Transduction Bruce Demple	191
in the Nucleus Enter Pygopus and Legless (hBcl9) Perspectives References CHAPTER 296 Cubitus Interruptus Sarah M. Smolik and Robert A. Holmgren Introduction	167	Introduction: Redox Biology Oxidative Stress Responses in Bacteria: Well-Defined Models of Redox Signal Transduction Responses to Superoxide Stress and Nitric Oxide: SoxR Protein Response to H ₂ O ₂ and Nitrosothiols: OxyR Protein Parallels in Redox and Free-Radical Sensing Themes in Redox Sensing References	
Protein Structure and Expression Patterns of Ci Regulation of Ci by Hedgehog Regulation of Ci by PKA Ci Transcriptional Regulation References CHAPTER 297		CHAPTER 301 Budding Yeast DNA Damage Checkpoint: A Signal Transduction-Mediated Surveillance System Marco Muzi-Falconi, Michel Giannattasio, Giordano Liberi, Achille Pelliccioli, Paolo Plevani, and Marco Foiani	, 197 ,
The Smads Malcolm Whitman Introduction Families: R-Smads, Co-Smads, and I-Smads Smad Oligomerization and Regulation by Receptors Transcriptional Regulation by Smads Down-Regulation and Cross-Regulation of Smads Function In Vivo: Gain of Function Loss of Function References	171	Introduction Sensing Downstream Events References CHAPTER 302 Finding Genes That Affect Signaling and Toleration of DNA Damage, Especially DNA Double-Strand Breaks Craig B. Bennet and Michael A. Resnick	203
Section C: Damage/Stress Response Albert J. Fornace, Jr., Editor CHAPTER 298 Complexity of Stress Signaling		Introduction Nature of DSB and Repair and Genetic Consequences Checkpoint Activation and Adaptation as Signaling Responses to DSBs	
and Responses Sally A. Amundson and Albert J. Fornace, Jr. Introduction: A Variety of Stresses Origin of Signals Signal Transduction Functional Genomics and Proteomics Approaches References CHAPTER 299 Signal Transduction in the	179	DNA Damage Signaling Networks Identifying Checkpoint Defects by Screening Radiation Sensitive Mutants Checkpoint Mutants Revealed through Screening DNA Replication Mutants Screening for Checkpoint Defects Screen for Altered Checkpoint and Adaptation Responto a Single DSB Other Screens for DNA Damage Checkpoint Pathway Genes Implications of DNA Damage Checkpoint	A nses
Escherichia coli SOS Response	185	Signaling	

References

Penny J. Beuning and Graham C. Walker

CHAPTER 303 Radiation Responses in Drosophila Naoko Sogame and John M. Abrams	213	CHAPTER 307 Abl in Cell Signaling Jean Y. J. Wang	249
Introduction Sensors and Transmitters Effectors Conclusions: What Can We Learn from the Drosophila Model? References		Introduction Functional Domains of Abl Proteins that Interact with Abl Abl in Signal Transduction Future Prospects References	
CHAPTER 304 Double-Strand Break Recognition and Its Repair by Nonhomologous End Joining ane M. Bradbury and Stephen P. Jackson introduction Repair of DSBs: Homologous Recombination and NHEJ Recognition of DNA DSBs	219	CHAPTER 308 Radiation-Induced Cytoplasmic Signaling Christine Blattner and Peter Herrlich Introduction Cytoplasmic Signaling Network Redox Sensitivity and Metal Toxicity: Toxic Agents Activate Signaling Pathways Activation of Signaling Components Primary Radiation Targets: DNA Damage versus	257
Signal Transduction DNA Repair Other Sensors and Transducers of DNA Damage New Factors in NHEJ Outure Prospects References CHAPTER 305		Cytoplasmic Signaling Other Signaling-Initiating Principles Conclusions References CHAPTER 309 Endoplasmic Reticulum Stress Responses	263
Role of ATM in Radiation Signal Transduction Martin F. Lavin, Shaun Scott, Philip Chen, Sergei Kozlov, Four Gueven, and Geoff Birrell Introduction Sensing Radiation Damage in DNA	225	David Ron Introduction ER Stress Defined The UPR in Yeast The UPR Is Metazoans Conclusions References	
ATM Signaling: Recognition of Breaks in DNA Checkpoint Activation Role of ATM in More General Signaling Perspective References		CHAPTER 310 The Heat-Shock Response: Sensing the Stress of Misfolded Proteins Richard I. Morimoto and Ellen A. A. Nollen	269
CHAPTER 306 Signaling to the p53 Tumor Suppressor hrough Pathways Activated by Genotoxic and Nongenotoxic Stresses Carl W. Anderson and Ettore Appella introduction	237	Introduction Transcriptional Regulation of the Heat-Shock Response Molecular Chaperones: Folding, Misfolding, and the Assembly of Regulatory Complexes Neurodegenerative Diseases: When Aggregation-Pron Proteins Go Awry References	ie
2053 Protein Structure Posttransitional Modifications to p53 Regulation of p53 Activity Activation of p53 by Genotoxic Stresses Activation of p53 by Nongenotoxic Stresses Conclusions		CHAPTER 311 Hypoxia-Mediated Signaling Pathways Albert C. Koong and Amato J. Giaccia Introduction	277
References		HIF-1 Signaling	

Signaling

References

Thomas Radimerski and George Thomas

Unfolded Protein Response Conclusions References		CHAPTER 316 Unfolded Protein Response: An Intracellul Signaling Pathway Activated by the	ar
CHAPTER 312 Regulation of mRNA Turnover by Cellular Stress Myriam Gorospe	283	Accumulation of Unfolded Proteins in the Lumen of the Endoplasmic Reticulum Randal J. Kaufman Introduction	311
Introduction mRNA Stability Stress-Activated Signaling Molecules that Regulate mRNA Turnover Conclusions References		UPR in Saccharomyces cerevisiae UPR Transcriptional Activation in Metazoan Species Physiological Role for the UPR in Mammals Future Directions References	
Section D: Post-Translational Control		CHAPTER 317 Regulation of mRNA Turnover Perry J. Blackshear and Wi S. Lai	319
Nahum Sonenberg, Editor CHAPTER 313		Introduction Current Models of mRNA Stability in Vertebrate Cells Presence of Instability Elements in Vertebrate mRNAs Effects of ARE Binding Proteins on mRNA	
RNA Localization and Signal Transduction Vaughan Latham and Robert H. Singer	293	Effects of ARE Binding Proteins on mRNA Turnover Regulation of TTP Activity in Cells Conclusion References	
Introduction Growth Factors Induce mRNA Localization Signaling from the Extracellular Matrix Induces mRN Localization mRNAs Localized via the Cytoskeleton mRNA Granule Movement in Neurons Regulation of mRNA Localizing Proteins GTPase Signals Regulating Actomyosin Interactions	A	CHAPTER 318 CPEB-Mediated Translation in Early Vertebrate Development Joel D. Richter Introduction	323
Are Involved in mRNA Localization Conclusion References		Mechanism of Translational Control CPEB and Early Development Conclusions References	
CHAPTER 314		CHAPTER 319	
Translational Control by Amino Acids		Translational Control in Invertebrate	
and Energy Tobia Schmelze, José L. Crespo, and Michael N. Hall	299		327
Introduction GCN System TOR Signaling Pathway References		Introduction Translational Control Targets Oskar to the Pole Plasm Translational Control Targets Nanos to the Pole Plasm	
CHAPTER 315 Translational Control and Insulin		Translational Control in the <i>Drosophila</i> Nervous System	

305

Growth

References

Role for Translational Control in Regulation

Translational Repression through MicroRNAs

CHAPTER 320 Role of Alternative Splicing During the Cell Cycle and Programmed Cell Death Chanseok Shin and James L. Manley	331	SCAP: Sterol Sensor and Escorter of SREBP from ER to Golgi Sterols Control Sorting of SCAP/SREBP into ER Vesicles ER Retention of SCAP/SREBP Conclusions	-
Introduction Apoptosis and Splicing Cell Cycle and Splicing Regulation References		References	
CHAPTER 321 NF90 Family of Double-Stranded RNA-Binding Proteins: Regulators of Viral and Cellular Function	335	CHAPTER 324 Endoplasmic Reticulum Stress Responses David Ron	359
OF VITAL AND CENTIAL FUNCTION Trevor W. Reichman and Michael B. Mathews Summary	333	Introduction Conclusion References	
Introduction Members of the NF90 Protein Family Domain Structure of NF90 Family Proteins Proteins that Interact with NF90 Nucleic Acid Binding Properties of NF90 Functions of NF90 Homologs Cellular Regulation of NF90 and NF45 Conclusions References CHAPTER 322 Signaling Pathways that Mediate Translational Control of Ribosome		CHAPTER 325 Signaling Pathways from Mitochondria to the Nucleus Zhengchang Liu and Ronald A. Butow Introduction Milestones in Mitochondrial Research Mitochondrial Signaling Aging and Retrograde Regulation Conclusions References	365
Recruitment of mRNA Nahum Sonenberg and Emmanuel Petroulakis	343	CHAPTER 326	
Introduction eIF4F Complex Formation Repressors of Cap-Dependent Translation Modulation of 4E-BP Phosphorylation FRAP/mTOR Phosphorylation of eIF4G and eIF4B Control of Cell Growth and Proliferation by eIF4E: Link to Cancer Conclusions References		Signaling During Exocytosis Lee E. Eiden Introduction Functional, Morphological, and Historical Aspects of Exocytosis and Stimulus-Secretion Coupling Secretion Begins with Secretagogues Secretagogues Act at Target Cell Receptors Calcium and Cyclic AMP: The Two Main Second Messengers for Secretion Calcium and the Regulation of Exocytosis	375
PART IV EVENTS IN INTRACELLULAR COMPARTMENTS Marilyn Farquhar, Editor		Calcium and the Regulation of Exocytosis Exocytosis and SNAREs Calcium and cAMP Sensors for Exocytosis Role of Signal Summation in Regulated Exocytosis	
CHAPTER 323 SREBPs: Gene Regulation through Controlled Protein Trafficking Peter J. Espenshade, Joseph L. Goldstein, and Michael S. B	353 rown	Role of PKC and Other PMA Targets in Regulated Secretion Negative Regulation of Secretion Upstream Regulation of Secretion Far Upstream Regulation of Secretion Conclusions and Future Outlook for Signaling in	
Introduction SREBPs: Membrane-Bound Transcription Factors		Exocytosis References	

Future Directions References

	_
Chapter 327	Chapter 331
Nonclassical Pathways of Protein	Apoptosis Signaling: A Means to an End 431
Export 393	Lisa J. Pagliari, Michael J. Pinkoski, and Douglas R. Green
Igor Prudovsky, Anna Mandinova, Cinzia Bagala, Raffaella Soldi, Stephen Bellum, Chiara Battelli, Irene Graziani, and Thomas Maciag	Introduction The End of the Road Caspase-8 Activation via Death Receptors
Introduction Fibroblast Growth Factor Export Pathways The Export of FGF-1 as a Multiprotein Complex Interleukin-1 Export Pathways Acidic Phospholipids and the Molten Globule Hypothesis The Potential Pathophysiological Implication of Nonclassical Release	Mitochondria and the Activation of Caspase-9 Mitochondrial Outer Membrane Permeabilization The Bcl-2 Family Cell Cycle versus Apoptosis Conclusions References
References	Chapter 332
	Signaling Down the Endocytic Pathway 441
CHAPTER 328	Jeffrey L. Benovic and James H. Keen
Regulation of Cell Cycle Progression 401	•
Clare H. McGowan	Introduction RTK Signaling from the Cell Surface
Introduction	RTK Signaling from Endocytic Compartments
Being There: Cyclins Define Cell Cycle Phase	GPCR Signaling Paradigms and Desensitization
Signals to Slow Processes: Regulation of Cdks by	Control of RTK and GPCR Trafficking Leading to
Inhibitory Proteins	Degradation
Cdks Are Positively and Negatively Regulated by	GPCR Activation of MAP Kinases
Phosphorylation	Endocytic Signaling in Developmental Systems
Degradation: The Importance of Being Absent	Signaling between Neuronal Cell Body and Terminal References
Location, Location, Location	Keletelices
Checkpoint Signaling References	
References	PART V
CHAPTER 329	CELL-CELL AND CELL-MATRIX
Endocytosis and Cytoskeleton 411	
Pier Paolo Di Fiore and Giorgio Scita	INTERACTIONS
•	E. Brad Thompson, Editor
Introduction	
Actin Dynamics and Endocytosis Role of Microtubule Cytoskeleton in Receptor Endocytosis	PART V
Physical and Functional Interactions of Dynamin and	Introduction
Dynamin-Interacting Proteins with the Actin Cytoskeleton	Brad Thompson
Integration of Signals in Endocytosis and Actin Dynamics	
by Small GTPases	Chapter 333
Conclusions	Overview of Cell-Cell and Cell-Matrix
References	Interactions 452
Creamon 220	E. Brad Thompson and Ralph A. Bradshaw
Chapter 330	-
Molecular Basis for Nucleocytoplasmic	References
Transport 419	Chapter 334
Gino Cingolani and Larry Gerace	Angiogenesis: Cellular and Molecular
Introduction	Aspects of Postnatal Vessel Formation 455
Transport Signals	Carla Mouta, Lucy Liaw, and Thomas Maciag
Transport Receptors	
The Small GTPase Ran Nuclear Pore Complex	Introduction Initiators of Angioganesis: Callular Metabolic and
Mechanism of Transport	Initiators of Angiogenesis: Cellular, Metabolic, and Mechanical

Vessel-Specific Requirements in Angiogenesis Cellular and Soluble Regulators

Coordination of Angiogenesis by Cellular and		Transcriptional Regulation	
Molecular Interactions		AP-1	
References		NFkB Transcription Factor	
C 225		Role of NFKB	
Chapter 335		Conclusions	
Signaling Pathways Involved		References	
in Cardiogenesis	463	CHAPTER 339	
Deepak Srivastava			
Tutor do ation		Cell-Cell and Cell-Matrix	
Introduction Cardiomyocyte and Heart Tube Formation			497
Cardiac Looping and Left-Right Asymmetry		L. F. Bonewald	
Patterning of the Developing Heart Tube		Introduction	
Myocardial Growth		Diseases of Bone	
Cardiac Valve Formation		Bone Cells and Their Functions	
Cardiac Outflow Tract and Aortic Arch Development		Mechanical Strain	
Conclusions		Hormone Responsible for Bone Development,	
References		Growth, and Maintenance	
Misionoes		Growth and Transcription Factors Responsible for Bon	e
Chapter 336		Development and Growth	
		Fibroblast Growth Factors	
Development and Regulatory Signaling	471	Bone Extracellular Matrix	
in the Pancreas	471	Conclusions	
Murray Korc		References	
Introduction			
Ontogeny of the Pancreas		<u>Chapter 340</u>	
Pancreatic Islet-Acinar Interactions		Cell-to-Cell Interactions in Lung	509
Cell-Cell and Matrix Interactions in the Endocrine		Joseph L. Alcorn	
Pancreas		-	
Matrix and Cell-Cell Interactions in the Exocrine Pan	creas	Introduction	
Conclusions		Lung Organogenesis and Development	_
References		Soluble Factors of Cell-to-Cell Interactions Involved in	.1
		Lung Injury	
Chapter 337		Conclusion References	
Tropic Effects of Gut Hormones in the		References	
Gastrointestinal Tract	477	Chapter 341	
B. Mark Evers and Robert P. Thomas			
		Mechanisms of Stress Response Signaling	
Introduction		and Recovery in the Liver of Young versus	ļ.
Tropic Effects of Gut Peptides in the Stomach, Small		Aged Mice: The p38 MAPK and SOCS	
Bowel, and Colon		Families of Regulatory Proteins	515
GI Hormone Receptors and Signal Transduction Path	iways	John Papaconstantinou	
Signaling Pathways Mediating the Effects of		Introduction	
Intestinal Peptides Conclusions		The p38 MAPK Pathway in Stress Response Signaling	OT .
References		SOCS Family of Negative Regulators of Inflammatory	_
References		Response	,
Chapter 338		Conclusions	
		References	
Integrated Response to Neurotrophic	40.	Aldred Control of the	
Factors	485	Chapter 342	
J. Regino Perez-Polo		Cell-Cell Signaling in the Testis and	
Introduction		-	531
Neural Cell Death		Ovary	JJI
The Neurotrophic Hypothesis		Michael K. Skinner	
Neurotrophins		Introduction	
Neurotrophin Receptors		Cell-Cell Signaling in the Testis	
Neurotrophin Signaling Pathways		Cell-Cell Signaling in the Ovary	

Apparatus

Tubulovascular Interactions: The Juxtaglomerular Apparatus and Tubuloglomerular Feedback

Conclusions References		Vasculotubular Communication Tubule-Tubule Communication: Paracrine Agents	
CHAPTER 343		Released from Epithelial Cells Interstitial Cell-Tubule Communication	
T Lymphocytes Rolf König and Wenhong Zhou	546	Conclusions References	
Introduction Signaling Receptors in T Cells form Dynamic Macromolecular Signaling Complexes Coreceptor and Costimulatory Proteins Modulate T-Cell Signaling Pathways Intracellular Signaling Pathways Induced by Antigen Stimulation of T Cells Conclusions References		CHAPTER 347 Prostate Jean Closset and Eric Reiter Introduction Development of the Prostate during Fetal Life The Adult Prostate The Prostate during Aging Conclusions References	591
CHAPTER 344		C 249	
Signal Transduction via the B-Cell Antigen Receptor: A Crucial Regulator of B-Cell Biology Louis B. Justement	555	CHAPTER 348 Retrograde Signaling in the Nervous System: Dorsal Root Reflexes William D. Willis	607
Introduction Initiation of Signal Transduction through the BCR Propagation of Signal Transduction via the BCR Conclusions References		Cell-to-Cell Signaling in the Nervous System Retrograde Signaling Neurogenic Inflammation Dorsal Root Reflexes as Retrograde Signals Conclusions References	
CHAPTER 345		References	
Signaling Pathways in the Normal and Neoplastic Breast Danica Ramljak and Robert B. Dickson	565	CHAPTER 349 Cytokines and Cytokine Receptors Regula Cell Survival, Proliferation, and	ting
Introduction Signaling Molecules: A Class of Growth Factors PI3K/Akt, MEK/Erk, and Stats: Major Proliferation/ Survival Molecules Downstream of Growth Factor Receptors in Breast Conclusions and Future Prospects References		Differentiation in Hematopoiesis Fiona J. Pixley and E. Richard Stanley	615
		General Aspects of Hematopoiesis Signaling through Cytokine Receptors Conclusions References	
CHAPTER 346		Chapter 350	
Kidney Elsa Bello-Reuss and William J. Arendshorst	573	Regulation of Bartlett Endogenous Stem Cells in the Adult Mammalian Brain:	
Overview of Kidney Functions and Cell-to-Cell Interactions		Promoting Neuronal Repair Rodney L. Rietze and Perry F. Bartlett	625
Vascular Endothelial Cells Vascular Smooth Muscle Cells Tubulovascular Interactions: The Juxtaglomerular Apparatus		Adult Neurogenesis Revealed Isolation and Culture of Neural Stem Cells Regulation of Stem Cell Differentiation into Neuron References	

Index