

Contents

Part I Metabolic Syndromes

1	Introduction	3
1.1	The Cellular Signaling Machinery Makes Homeostasis Possible	4
1.2	Inflammation Is Present in Diseases	4
1.3	Cholesterol Together with Inflammation Promotes Atherosclerosis	6
1.4	Signaling Pathways Responsible for Maintaining Cellular Homeostasis Are Uncovered and Explored	6
1.5	Biophysical Techniques Provide Detailed Information on the Three-Dimensional Structure of Macromolecules	7
1.6	Signaling Pathways Have Been Illuminated Through Intensive Efforts Spanning the Last 50 Years	8
1.7	Mutated, Misfolded Proteins Cause Cancer	9
1.8	The Microenvironment Is an Important Ingredient in Cancer Metastasis	10
1.9	Neurons Are Cells Highly Specialized for Long-Range Signaling	12
1.10	Amyloids Are an Essential Ingredient in Many Diseases	12
1.11	Reactive Oxygen and Nitrogen Species Carry Out Signaling in Ways That Contribute to Health and Disease	15
	Further Reading	15
2	Energy Balance	19
2.1	Hormonal Signaling by the Endocrine Pancreas	21
2.2	In Response to Signals from the Pancreas, the Liver Maintains Glucose and Lipid Homeostasis	22
2.3	Energy in the Form of Lipids Is Stored and Released When Needed in Adipose Tissue	24
2.4	Adipose Tissue Functions as an Endocrine Organ	25

2.5	Ghrelin Released by Endocrine Cells in the Stomach Acts in Short-Term Feeding and Long-Term Energy Management	26
2.6	Satiation Signals Are Sent by Cells in the Gastrointestinal Tract	26
2.7	Brown Adipose Tissue Carries Out Adaptive (Diet-Induced and Cold-Induced, Nonshivering) Thermogenesis	27
2.8	Muscle Cells and β -Oxidation	29
2.9	AMPK Is an Intracellular Energy Sensor and Regulator	31
2.10	AMPK Is Activated by Upstream Kinases and by Depleted Energy Supply as Indicated by Increased AMP/ATP Ratios	33
2.11	The Hypothalamic Network Provides Feedback Signals to Peripheral Tissues	35
2.12	Leptin Signaling and Regulation of Energy Balance in the Hypothalamus	37
2.13	Ghrelin Signaling and Regulation of Energy Balance in the Hypothalamus	39
	Further Reading	40
3	Insulin Signaling and Type 2 Diabetes	45
3.1	Type 2 Diabetes Develops in a Series of Stages from Overnutrition	46
3.2	Adipose Tissue Functions as an Immune Organ	47
3.3	Metabolic Overload Occurs in Energy-Responsive Tissues	48
3.4	Signal Transduction Begins with the Insulin Receptor and Its Substrate Proteins	50
3.5	Phosphoinositide-3-OH Kinase (PI3K) and the PTEN Lipid Phosphatase	52
3.6	Activation of Protein Kinase B (PKB) and Protein Kinase C (PKC)	54
3.7	GLUT4 Transport Biomechanics and Regulation	56
3.8	The TOR Cassette Is the Downstream Target of Akt Signals	58
3.9	Feedback Regulation of Akt by TORC2 and IRS by TORC1/S6K	60
3.10	Insulin Resistance Develops from Inflammation and Metabolic Overload	60
3.11	Glucose-Stimulated Hormone Release by Pancreatic Islet Cells	63
3.12	K _{ATP} Channels and Their Regulation by Cellular Fuel Status	65
3.13	Islet β -Cell Failure and Diabetic Complications	66
	Further Reading	67

4	Metabolic Program Execution and Switching	71
4.1	Nuclear Receptors Are Ligand-Activated Transcription Factors	71
4.2	Nuclear Receptors Contain Five or Six Domains	73
4.3	The CAR Activates and Deactivates in a Manner Distinct from Other Nuclear Receptors	74
4.4	Peroxisome Proliferator-Activated Receptors Are Lipid Sensors and Effectors	75
4.5	Nuclear Receptors Require Coactivators and Corepressors	77
4.6	PGC-1 Scaffold Protein in Regulation of Lipid Homeostasis	80
4.7	FoxOs Mediate Survival, Metabolic, and Stress Responses	80
4.8	14-3-3 Protein Function as Small, Mobile Phosphoprotein Binding Modules	82
4.9	Gluconeogenesis in the Liver Is Stimulated by Glucagon and Repressed by Insulin	83
4.10	Catecholamine Signaling Targets PGC1 α to Promote Diet-Induced Thermogenesis in Brown Adipose Tissue	85
4.11	Caloric Restriction Extends Lifespan by Activating Protective Stress Responses	86
4.12	SIRT1 Promotes Fatty Acid Oxidation in Liver and Skeletal Muscle	87
	Further Reading	88
5	Cholesterol	91
5.1	Membrane Lipids Form Gels and Liquid States	91
5.2	Feedback Regulation of Cholesterol Synthesis by Insigs	94
5.3	Feedback Regulation of Cholesterol Synthesis by SREBPs	95
5.4	SREBPs, Liver X Receptors, and Farnesoid X Receptors Regulate Transcription	97
5.5	Lipoproteins Are Carriers of Cholesterol and Triglycerides	98
5.6	Apolipoproteins are Amphipathic, Lipid-Binding Constituents of the Lipoproteins	99
5.7	Cholesterol Comes in Two Forms – As a Sterol, i.e., as a Free Cholesterol (FC) Molecule, and as a Cholesterol Ester (CE)	102
5.8	ABC Transporters Export Cholesterol from Macrophages	103
	Further Reading	104

6	Atherosclerosis	107
6.1	The Arterial Wall Consists of Three Layers	107
6.2	Cells Are Continually Subjected to Forces	109
6.3	Atherosclerotic Lesions Occur Preferentially in Regions of Disturbed Blood Flow	110
6.4	Cells Utilize Multiple Mechanotransduction Pathways That Convey Information About Blood Flow	112
6.5	Mechanotransduction Pathways Relay Information About Blood Flow to Endothelial Caveolae and Nitric Oxide Synthase	112
6.6	oxLDL Is Atherogenic and Acts in Opposition to eNOS and NO	113
6.7	Cell Adhesion Molecules and Chemokines Mediate Leukocyte Migration into Sites of Inflammation	115
6.8	Leukocyte Migration Occurs Through a Multistep Adhesion Cascade	117
6.9	Selectins Are Key Mediators of Leukocyte Tethering and Rolling	118
6.10	Slip and Catch Bonds Play Important Roles in Selectin-Mediated Rolling	119
6.11	Leukocyte Arrest Through the Joint Actions of Chemokines and Integrins	121
6.12	Epithelial Cell-to-Cell Adhesions Are Maintained by Junctional Complexes	123
6.13	Leukocytes Enter the Intima by Passing In-Between Epithelial Cells and by Passing Through Them	125
6.14	Rupture of the Fibrous Cap and Not the Lesion Itself Causes Thrombosis	126
	Further Reading	128
7	Chronic Inflammation	131
7.1	The NF- κ B Signaling Node Consists of IKKs, I κ Bs, and NF- κ Bs	132
7.2	Protein Ubiquitination Plays a Central Role in Cellular Signaling	135
7.3	TNF α Signaling Occurs Through Complex I and Complex II	137
7.4	Reactive Oxygen Species (ROS) Influences the Choice Between Survival and Death	138
7.5	Toll-like Receptor 4 Responds to Bacterial Lipopolysaccharides and Mammalian Lipids	139
7.6	Downstream and into the Nucleus with NF- κ Bs	141
7.7	Glucocorticoids Terminate Inflammatory Responses and Restore Homeostasis	142

7.8	LXRs and PPAR γ in Transrepression of Inflammation Through SUMOylation	143
7.9	The Local Microenvironment Is a Key Organizational Unit in Health and Disease	145
7.10	The Inflammatory Response Is a Biphasic One with Distinct Clear Up and Reconstruction Phases	146
7.11	Macrophages Are Inflammatory Cells with Key Roles in the Body's Response to Infection and Injury	147
7.12	Fibroblasts Are Connective Tissue Cells	149
7.13	Mesenchymal Stem Cells Are Located Throughout the Body	150
	Further Reading	150
8	Redox Signaling	155
8.1	Hydrogen Peroxide and Nitric Oxide Are Signaling Molecules	156
8.2	Nox Enzymes	157
8.3	Oxidation of Sulfhydryls and Hydrogen Peroxide Signaling	159
8.4	Nitric Oxide Synthases and Nitric Oxide Signaling	162
8.5	The Frank-Starlings Law and Excitation–Contraction Coupling	164
8.6	Transcriptional Regulation of the Metabolic Programs	166
8.7	Inappropriate S-Nitrosylation Contributes to Neurodegenerative Disorders	168
8.8	The Electron Transport Chain Can Generate Reactive Oxygen Species	170
	Further Reading	172

Part II Cancer

9	The Cell Cycle	179
9.1	The Cell Cycle Has Four Phases	182
9.2	Ubiquitin-Mediated Proteolysis Is a Key Part of the Cell Cycle Machinery	183
9.3	Several Families of Activators and Inhibitors Are Part of the Cell Cycle Engine	184
9.4	The Retinoblastoma Proteins and E2F Transcription Factors Are Downstream Cell Cycle Effectors at the G1/S Transition	185
9.5	Cell Cycle Effectors at the G2/M Transition	187
9.6	The SCF and APC/C Are Large Multisubunit Complexes	188
9.7	Mathematical Modeling Is an Essential Tool in Understanding Signaling Pathways and Networks	189
9.8	The Goldbeter Model of Entry and Exit from Mitosis	192

9.9	Multiple Positive and Negative Feedback Regulate the Progression Through the Cell Cycle	194
9.10	Multisite Phosphorylation Helps Ensure the Correct Ordering of Events	196
9.11	Traversing the Cell Cycle with the APC and SCF	196
	Further Reading	197
10	Cell Cycle Checkpoints and DNA Damage Repair	201
10.1	The G1/S Checkpoint Pathway	202
10.2	Formation of IRIFs and Activation of ATM	203
10.3	Mediators Amplify the ATM Signal	205
10.4	Intra-S Phase and G2/M Checkpoints	206
10.5	Formation of SDSCs and Activation of ATR	207
10.6	Structure and Posttranslational Modifications of Checkpoint Proteins	208
10.7	p53 Structure and Function	210
10.8	Restoration of p53 Function by Second-Site Suppressors	212
10.9	Special Domains Mediate Protein–Protein Interactions and Chromatin Binding by Proteins that Function at the Apex of the Checkpoint and Repair Pathways	213
10.10	Base Excision Repair	214
10.11	Nucleotide Excision Repair	216
10.12	Mismatch Repair	216
10.13	Repair Proteins Diffuse Laterally in One-Dimension Along DNA	217
10.14	There Are Two Double-StrandBreak Repair Systems	218
10.15	The Mre11–Rad50–Nbs1 (MRN) Complex Is Involved in DNA Damage Sensing, Signaling, and Repair	220
10.16	Completing the Repair and Terminating the Checkpoint	221
	Further Reading	222
11	Apoptosis and Senescence	227
11.1	Pathways to Apoptosis – Extrinsic and Intrinsic	228
11.2	Bcl2 Proteins Mediate the Apoptotic Balance	230
11.3	Sequestration and Release of Cytochrome c	232
11.4	Damage-Induced Apoptosis via p53 Transcription and Mitochondrial Actions	233
11.5	Cells That Are Healthy Do Not Have an Unlimited Capacity to Divide	234
11.6	Telomere Structure and Capping Proteins	234

11.7	Cancer Cells Increase Their Production of Telomerase, an Enzyme That Immortalizes the Cells	235
11.8	Regulation of Replicative Senescence by p53 and pRb	236
11.9	DNA Damage and Oncogene-Induced Senescence	237
11.10	A Model or Two of Oncogene-Induced Stress	238
11.11	p53 Undergoes Posttranslational Modifications Including Phosphorylation, Acetylation, and Ubiquitination at Multiple Sites	240
11.12	Heterochromatin Formation Provides a Route to Oncogene-Induced Senescence	241
11.13	The Retinoblastoma Protein Helps Establish the Senescent State by Mediating Heterochromatin Formation	243
	Further Reading	244
12	Epigenetics	249
12.1	Nucleosomes and Chromatin Structure	250
12.2	Epigenetic Marks	251
12.3	DNA Methylation	253
12.4	Polycomb and Trithorax Group Proteins	254
12.5	Histone Acetylation and Deacetylation	254
12.6	Histone Methylation and Demethylation	255
12.7	Reading Out Histone Marks by Recognition Modules	256
12.8	Cooperative Actions by Histone Modification Enzymes and DNA Methyltransferases Can Silence Genes and Lead to Cancer	259
12.9	Recently Discovered Small Noncoding RNAs (ncRNAs) Regulate Gene Expression	260
12.10	Atomic-Level Studies of Dicer and Slicer Provide Crucial Insights into ncRNA Function	262
12.11	MicroRNAs and Cancer	264
12.12	Induced Pluripotent Stem Cells	266
	Further Reading	267
13	Tumor Growth	271
13.1	Growth and Survival Signaling Pathways	271
13.2	Receptor Activation Leads to Recruitment of Molecular Adaptors to Docking Sites	273
13.3	Ras and Other Small GTPases Link Adaptors to Downstream Signaling Elements	275
13.4	Many of the Growth Signaling Proteins Function as Oncogenes	276
13.5	MAP Kinase Signaling Modules	278
13.6	The MAP Kinase Modules and Their Substrates Function as Dynamical Circuits	280

13.7	Active and Inactive Conformations of Protein Kinases	281
13.8	Oncogene Addiction	282
13.9	Target-Based Anticancer Therapies	283
13.10	Myc Protein Structure and Function	284
13.11	Phosphorylation and Polyubiquitination Sculpt Myc-Mediated Gene Transcription	285
13.12	Regulation of Cellular Growth by Ras, Erk, and Myc	286
13.13	Regulation of Cellular Proliferation by Myc	287
	Further Reading	288
14	Tumor Metabolism	291
14.1	The Central Growth Network of the Cell Is Organized About the mTOR Cassette	292
14.2	AMPK Supplies a Gating Signal Indicative of Energy Balance	293
14.3	Cells Halt Growth in Response to Hypoxia and Other Cellular Stresses	293
14.4	Regulation of Cell Growth by Amino Acid Starvation Signaling to mTOR	295
14.5	Regulation of the Translation Initiation Complex by mTOR	296
14.6	Starvation and Autophagy	298
14.7	p53 Modulation of Metabolism Is One of Its Barrier Functions	300
14.8	The PTEN Tumor Suppressor Acts at the Plasma Membrane and in the Nucleus	302
14.9	Mutations and Disturbed Redox Balance Deactivate PTEN	303
14.10	HIF Transcription Factors Sense and Respond to Low Oxygen Conditions	304
14.11	HIFs Regulate Cellular Metabolism and Drive the Glycolytic Shift	306
14.12	Hexokinase II and Akt Drive the Glycolytic Shift and Prevent Apoptosis in Tumors	307
	Further Reading	309
15	Metastasis	313
15.1	Tumor Growth and Metastasis Are Community Affairs . . .	314
15.2	Macrophages and Fibroblasts Direct Invasion and Intravasation	316
15.3	The SDF-1/CXCR4 Axis Is a Central Participant in Metastasis	317
15.4	Focal Adhesions and Metastatic Migration	318
15.5	Receptor Cooperativity and Src Signaling	320
15.6	The Transforming Growth Factor- β Pathway	322

15.7	TGF- β Promotes Cytostasis	325
15.8	The Wnt Pathway	326
15.9	The Epithelial to Mesenchymal Transition	327
15.10	MicroRNAs and Transcription Repressors Jointly Regulate E-Cadherin Expression	329
15.11	MicroRNAs Act as Metastasis Repressors and Activators	331
15.12	Stem Cells and Cancer Stem Cells	331
15.13	Changing Views About Metastatic Spread	332
15.14	The Notch Pathway	333
15.15	The Hedgehog Pathway in <i>Drosophila</i>	335
15.16	The Hedgehog Pathway in Mammals	336
15.17	Bone Metastasis Is a Seed-and-Soil Exemplar	338
	Further Reading	339

Part III Neurodegeneration

16	Protein Folding, Misfolding, and Aggregation	345
16.1	Proteins Spontaneously Fold into Their Native State Based Solely on Their Primary Amino Acid Sequence	348
16.2	Protein Folding Can Be Described in Terms of an Energy Landscape Dominated by a Folding Funnel	349
16.3	Some Landscapes Are Smooth While Others Are Rugged	351
16.4	Proteins, Especially Those Involved in Signaling, Often Fold into Nonglobular, Extended Conformations	352
16.5	Dialysis-Related Amyloidosis Is Brought on by Partial Unfolding and Aggregation of β -2 Microglobulin	354
16.6	β Cell Failure and Amyloid Formation in Type 2 Diabetes Is Brought on by Amylin Misfolding and Aggregation	357
16.7	Some Proteins Have Native States That Are Metastable and Not at a Global Minimum in the Free Energy	357
16.8	β -Sheet Conformational Variations Underlie the Prion Strains and Disease Potential	358
16.9	Strains and Transmissibility	361
16.10	General Observations on How Proteins Fold into Alternative Disease-Causing Structures Characterized by Cross- β -Sheets	362
	Further Reading	364
17	Alzheimer's Disease	369
17.1	Generation of the Amyloid β Protein	370
17.2	Removal Through Degradation and Clearance	373

17.3	Folding Physics, Metal Homeostasis, and Redox Chemistry	375
17.4	Normal Physiological Function of the A β Protein at the Synapse	376
17.5	Action of the A β Oligomers at the Synapse – Aberrant LTD	377
17.6	The Local Microenvironment Contains Neurons, Astrocytes, and Microglia	379
17.7	Microglia Respond to Amyloid Plaque Buildup by Mounting an Inflammatory Response	380
17.8	Inflammatory and Synaptic Cytokines Are Released by Microglia and Astrocytes.	382
17.9	Tau Hyperphosphorylation and Formation of the Tangles	384
	Further Reading	387
18	Chaperones, Endoplasmic Reticulum Stress, and the Unfolded Protein Response	391
18.1	The Cellular Complement of Molecular Chaperones.	392
18.2	Hsp70 Structure and Function	393
18.3	Hsp90 Structure and Function	394
18.4	Heat Shock Factor 1 Is a Master Regulator of Protein Homeostasis	396
18.5	Folding, Processing, and Maturation of Membrane and Secreted Proteins	397
18.6	N-Linked Glycan Processing	399
18.7	The Unfolded Protein Response.	401
18.8	ERAD and the Sec61 Translocon	404
18.9	The p97 Motor Protein Is a Molecular Chaperone Required for ERAD	405
	Further Reading	407
19	Parkinson's Disease	411
19.1	α -Synuclein Is a Presynaptic Protein	414
19.2	Abnormalities and Toxicity Result from α -Synuclein Misfolding and Aggregation.	414
19.3	Oxidative Damage Is a Cause of α -Synuclein Aggregation and PD.	415
19.4	Parkin Is an E3 Ubiquitin Ligase	416
19.5	Protein Carbonylation and UCH-L1	417
19.6	PINK1 Is a Neuroprotective Serine/Threonine Kinase	417
19.7	DJ-1 Protects Against Oxidative Stress	418
19.8	LRRK2 Is a ROCO Family Member and Mutations in This Protein Are Most Strongly Associated with PD	419
19.9	HtrA2/Omi Removes Misfolded Proteins	420

19.10	The Pathway Is Illuminated	421
19.11	Proteasome Organization	422
19.12	Cellular Garbage Collection and the Aggresomal – Autophagic Railway	424
19.13	Histone Deacetylase 6 Mediates Transport Along the Disposal Railway	425
	Further Reading	426
20	Huntington's Disease and Amyotrophic Lateral Sclerosis	431
20.1	Huntington's Disease Is an Expanded PolyQ Repeat Disorder	432
20.2	The Structure of the Huntingtin Protein Is That of a Multipurpose Signaling Organizer	434
20.3	Synaptic Terminal Interactions Occur	434
20.4	Impaired Fast Axonal Transport Happens	436
20.5	Zipper, Aggregation, Fibrils, Inclusion Body Formation, and Toxicity	436
20.6	The Ubiquitin-Proteasome System Regulates Synaptic Transmission and This Function Is Impaired by Mutant Htt	438
20.7	Impaired Transcription: CBP and PGC-1 – and Mitochondrial Dysfunction	439
20.8	Structure and Folding of the Superoxide Dismutase Protein SOD1	440
20.9	SOD1 Mutations and Aggregation	441
20.10	Impaired Fast Axonal Transport and Retraction of Axons from Synapses	442
20.11	A Model for Amyotrophic Lateral Sclerosis	443
20.12	Acceleration of ALS Through Interactions Between Neurons and Other Cellular Residents of Its Microenvironment	444
20.13	PolyQs, Mutant SOD1, and Impaired ERAD	446
20.14	Mutations in Genes Other Than That for SOD1 Can Cause fALS	447
20.15	Interlocking Signaling Networks Underlie Health and Disease	449
	Further Reading	450
	Index	455



<http://www.springer.com/978-0-387-98172-7>

Cellular Signaling in Health and Disease

Beckerman, M.

2009, XVIII, 470 p. 193 illus., Hardcover

ISBN: 978-0-387-98172-7