

CONTENTS

Preface	xii
1. Autocrine Transformation: Cytokine Model	1
<i>James A. McCubrey, Xiao-Yang Wang, Paul A. Algate, William L. Blalock and Linda S. Steelman</i>	
Abstract	1
Cytokine Regulation of Growth	1
2. Signal Transduction Pathways:	
Cytokine Model	17
<i>James A. McCubrey, William L. Blalock, Fumin Chang, Linda S. Steelman, Steven C. Pohnert, Patrick M. Navolanic, John G. Shelton, Paul E. Hoyle, Phillip W. Moye, Stephanie M. Oberhaus, Martyn K. White, John T. Lee and Richard A. Franklin</i>	
Abstract	17
Cytokine-Induced Signal Transduction Resulting in Growth and the Prevention of Apoptosis	17
Adaptor Proteins that Couple Receptors with Downstream Pathways	19
The Jak-STAT Pathway	19
The PI3K/Akt Pathway	22
The Ras/Raf/MEK/ERK Signal Transduction Pathway	22
The Ras/Raf/MEK/ERK Pathway: Downstream Kinase Activation	26
Interactions Between the Raf/MEK/ERK and the PI3K/Akt Pathways	28
The Ras/Raf/MEK/ERK Pathway: A Tether Enhancing Signal Transduction	28
The Ras/Raf/MEK/ERK Pathway: Regulation of Downstream Transcription Factors	28
Induction of Autocrine Gene Expression by Altered Raf/MEK and PI3K/Akt Expression	29
Mutations of Ras/Raf/MEK/ERK Cascade which Result in Neoplasia	29
Regulatory Phosphatases of the Ras/Raf/MEK/ERK Pathway	29
Alternative MAPK Pathways Activated by Stress	31
Default Pathways which Dampen Signaling	31
Jak/STAT Inhibitors	33
PI3K/p70S6K Inhibitors	33
Ras/Raf/MEK/ERK Pathway Inhibitors	33
PKC Inhibitors	33
Cytokine Regulation of Cell Cycle Progression	34
Links Between the Ras/Raf/MEK/ERK Pathway and Cell Cycle Proteins	34
Cytokine Regulation of Apoptosis and Cell Death	34
Apoptotic Mediators: The Caspases	34

Roles of Bcl-2 Family Members in Cytokine-Mediated Regulation of Apoptosis	35
Mitochondrial Regulated Apoptosis	35
Interactions Between Cytokine Signaling Pathways and Apoptosis	36
Phosphorylation of Bcl-2: Positive and Negative Effects	36
Future Remarks	36
Acknowledgments	37
3. The Restriction Point of the Cell Cycle	52
<i>Mikhail V. Blagosklonny and Arthur B. Pardee</i>	
Mitogen-Dependent and -Independent Phases of the Cell Cycle	52
The Restriction Point	52
In Search of Mediators of the Restriction Point	53
Cyclins: From Mitogen Signaling to the Restriction Point	54
The Restriction Point: a Knot of Mitogen and Inhibitory Signaling	55
Growth Arrest versus Proliferation	57
From Restriction- to “Check”-Points	58
The Restriction Point and G1 Checkpoint	59
The Restriction Point and Therapy	60
4. DNA Damage, Cell Cycle Control and Cancer	65
<i>Jens Oliver Funk, Temesgen Samuel and H. Oliver Weber</i>	
Abstract	65
Introduction	65
Origins of DNA Damage	66
DNA Damage of Intrinsic Origin	66
DNA Damage of External Origin	66
Upstream DNA Damage Signaling	66
ATM-Dependent Signaling Pathways	67
CHK2—The Next Line of Defense	67
p53—The Core of the DNA Damage Pathways	68
Regulatory Effects Converging on p53	69
The G1/S Checkpoint	70
p21CIP1—A Two-Tailed Cell Cycle Regulator	70
The G2/M Checkpoint	71
Control of the Unperturbed G2/M Transition	71
Regulation of the CDC25C Phosphatase	72
DNA Damage and the G2/M Transition	72
Links to Cancer and Genetic Instability	73
5. DNA-Damage-Independent Checkpoints from Yeast to Man	79
<i>Duncan J. Clarke, Adrian P.L. Smith and Juan F. Giménez-Abián</i>	
Abstract	79
Budding Yeast versus Higher Eukaryotes	79
S-Phase Checkpoint	81
Topoisomerase II-Dependent Checkpoint	86

Checkpoint Control in Prophase	87
Spindle Assembly Checkpoint	87
Checkpoint Control of Mitotic Exit	93
Oncological Implications of Mitotic Checkpoint Homologs	99

6. The Regulation of p53 Growth Suppression 106

Ronit Vogt Sionov, Igal Louria Hayon and Ygal Haupt

Abstract	106
Introduction	106
Regulation of p53	107
Regulation of Intracellular Distribution of p53	110
p53-Mediated Growth Regulatory Functions	112
The Choice Between Growth Arrest and Apoptosis	115
Cell Type-Dependence	116

7. Functional Interactions Between BRCA1 and the Cell Cycle 126

Timothy K. MacLachlan and Wafik El-Deiry

Introduction	126
BRCA1 Protein and mRNA during the Cell Cycle	126
Subcellular Localization	127
Activity at Cell Cycle Checkpoints	129
Interactions with Cell Cycle Proteins	130
Transcription of Cell Cycle Genes	131
Conclusion	132

8. The Role of FHIT in Carcinogenesis 135

Yuri Pekarsky, Kay Huebner and Carlo M. Croce

Abstract	135
Chromosomal Changes in Cancer	135
FHIT Loci is the Target of Chromosomal Abnormalities at 3p14.2 ..	136
Inactivation of FHIT mRNA and Protein Expression in Cancer.	137
The Tumor Suppressor Activity of FHIT	138
Toward Fhit Function	139
Conclusions	140

9. Hypoxia and Cell Cycle 143

Rachel A. Freiberg, Susannah L. Green and Amato J. Giaccia

Introduction	143
Cell Cycle and Check Points	144
Hypoxia-Induced Arrest	146
Mechanisms Underlying Cell Cycle Arrest By Hypoxia	147
Hypoxia-Induced Inhibition of CDK2 Activity and Resistance to Chemotherapy	151
Acknowledgments	152

10. G2 Checkpoint and Anticancer Therapy	155
<i>Zoe A. Stewart and Jennifer A. Pietsenpol</i>	
Abstract	155
Introduction	155
G2 Checkpoint Activation	157
G2 Checkpoint Maintenance	162
Modulation of the G2 Checkpoint—Therapeutic Implications	165
Future Directions	169
Acknowledgments	169
11. p53, Apoptosis and Cancer Therapy	179
<i>Rosandra Kaplan and David E. Fisher</i>	
Abstract	179
Introduction	179
p53's Emergence as a Key Death Regulator	181
Clinical Aspects of p53	183
Cell Cycle Arrest	184
Apoptosis	184
Regulating p53 Activation in the Stress Response	187
Cell Cycle Arrest vs Death	187
Therapy	188
12. Non-Apoptotic Responses to Anticancer Agents: Mitotic Catastrophe, Senescence and the Role of p53 and p21	196
<i>Igor B. Roninson, Bey-Dih Chang and Eugenia V. Broude</i>	
Abstract	196
Can Apoptosis Account for Tumor Cell Response to Anticancer Agents?	196
p53 as a Negative Regulator of Mitotic Catastrophe	199
Induction of Senescence by DNA-Damaging Agents	200
Role of p53 and p21 in Damage-Induced Senescence and Abnormal Mitosis	202
Paracrine Activities of Senescent Cells: Implications for Treatment Outcome and Side Effects of Cancer Therapy	203
Mitotic Catastrophe and Senescence as Target Responses in Cancer Treatment	203
13. Small Molecule Inhibitors of Cyclin-Dependent Kinases	208
<i>Geoffrey I. Shapiro</i>	
Introduction	208
Flavopiridol	208
The Paullones	219
Purine Derivatives	220
UCN-01	221
Novel Selective Cdk Inhibitors	226
Conclusion	228

14. Cell Cycle Molecular Targets and Drug Discovery	235
<i>John K. Buolamwini</i>	
Abstract	235
Introduction	235
Events in Cell Cycle Progression	236
Regulatory Pathways	237
Oncogenic Cell Cycle Targets	239
Cell Cycle Molecular Target-Based Cancer Drug Discovery	239
Cancer Drug Development of Small Molecule CDK Inhibitors	241
Other Targets	241
Index	247