CONTENTS

CONTRIBUTORS xi
PREFACE xv

PART 1 MOLECULAR AND STRUCTURAL ASPECTS 1

1 Structural Bases of Protein Kinase CK2 Function and Inhibition 3
Karsten Niefind and Roberto Battistutta
Introduction 3
Basic Structure/Function Relationships of CK2 8
CK2 Inhibitors 37
Conclusions and Outlook 60
Acknowledgments 61

2 The Interactome of Protein Kinase CK2 76
Mathias Montenarh and Claudia Götz
Introduction 76
From the Outside to the Inside: Interaction of CK2 with Membrane Proteins 78
Regulating Gene Expression: Interaction of CK2 with Components of Signaling Cascades, Transcription Factors and DNA Modifying Enzymes 82
Mastering Nucleic Acid Functions: Interaction of CK2 with Proteins of the Replication, Transcription, and Translation Machinery of the Cell 87
Let It Roll: Interaction of CK2 with Cell Cycle Regulatory Proteins 90
Guardian Angels: Interaction of CK2 with Proteins That Maintain the Cellular Integrity 93
Live and Let Die: Interaction of CK2 with Proteins of the Apoptotic Pathway 96
Highways in the Cell: Interaction of CK2 with the Cytoskeleton and Motor Proteins 96
Collaborating with the Enemy: Interaction of CK2 with Proteins Implicated in Viral Infections 98
Last But Not Least: Miscellaneous 99
Concluding Remarks 101

3 CK2 Contribution to the Generation of the Human Phosphoproteome 117
Luca Cesaro and Mauro Salvi
Kinases Contribution to the Human Phosphoproteome 117
CK2 Substrate Specificity 118

COPYRIGHTED MATERIAL
CONTENTS

Subphosphoproteomes of Proteins with Specific Functions 122
Subphosphoproteomes of Cellular Compartments 123
Absolute Quantification of Yeast Phosphoproteome Reflects the Constitutive Activity of CK2 125
Conclusions 125
Acknowledgments 126

PART 2 FUNCTIONAL ASPECTS 129

4 CK2 in Embryonic Development 131
Laura Macias Alvarez, Jesus Revuelta-Cervantes, and Isabel Dominguez
CK2 in Yeast Biology 131
CK2 in Invertebrate Development 135
CK2 in Vertebrate Development 139
CK2 in Plant Development 148
CK2 in Animal Developmental Signaling Pathways 149
Discussion 155
Outlook 157
Acknowledgments 158

5 Protein Kinase CK2: At the Crossroads of Pathways Controlling Cell Proliferation and Survival 169
Michelle Gabriel and David W. Litchfield
General Introduction 169
Protein Kinase CK2 170
CK2 in Cancer 171
Involvement of CK2 in Signaling Pathways Controlling Proliferation and Death 172
Concluding Remarks 182
Acknowledgments 183

6 The Role of Protein Kinase CK2 in the p53 Response 190
David W. Meek
Protein Kinase CK2 190
The p53 Network 191
The Interaction Between p53 and CK2 192
Regulation of p53 by Phosphorylation of Ser392 193
Proposed Mechanism for Regulation of p53 Phosphorylation at Ser392 (the “CK2” Site) 194
Phosphorylation of p53 by CK2 in a Physiological Context? 196
A Broader Role for CK2 in Regulating the p53 Network? 197
7 The Pivotal Role of CK2 in the Kinome-Targeting Hsp90 Chaperone Machinery

Yoshihiko Miyata

Protein Kinase CK2
Hsp90: A Major Molecular Chaperone
Co-Chaperones That Regulate Hsp90 Function
Hsp90 and Signaling Protein Kinases
Phosphorylation and the Regulation of Hsp90 by CK2
Phosphorylation of Cdc37 by CK2
A Crucial Role of CK2-Dependent Phosphorylation in the Functional Regulation of Cdc37
Regulation of the Cdc37 Phosphorylation Cycle
Regulatory Phosphorylation of FKBP52 by CK2
Phosphorylation of p23 by CK2
Targeting the CK2-Cdc37-Hsp90 Trinity for Cancer Chemotherapy
Conclusion

8 CK2: A Global Regulator of Cell Survival

Barbara Guerra and Olaf-Georg Issinger

CK2 and Cell Survival: Strategies, Methods, and Techniques for Exploring Its Role
CK2 and Cellular Death
Role of CK2 in DNA Damage
Role of the Individual CK2 Subunits in Cell Survival
CK2 Status in Non-neoplastic Cells
CK2 Activity and Expression in Neoplasia
CK2 in Heterotransplanted Tumors in Nude Mice
CK2 Holoenzyme and Its Subunits
Tumor Hypoxia
Conclusion

9 Specific Features of Plant CK2

Marta Riera, Isabel Cristina Vélez-Bermúdez, Tommaso Legnaioli, and Montserrat Pagès

Introduction
CK2α Catalytic Subunits
CK2β Regulatory Subunits
CK2 Holoenzyme
Physiological Role of CK2 in Plants

PART 3 CK2 AND NEOPLASIA

10 The Oncogenic Potential of CK2

David C. Seldin and Esther Landesman-Bollag

Introduction
CK2 Overexpression in Human Cancer
Unbalanced Expression of CK2 Subunits Is Correlated with Hypoxia and EMT-Related Markers 366
CK2β Subunit Silencing Induces EMT-Like Morphological Changes 367
Gene Expression Profiling 373
CK2β Silencing Triggers Snail1 Induction 373
Overexpression of SIX1 in CK2β-Depleted Cells 374
Conclusions 375
Acknowledgments 377

15 CK2 as a Logical Target in Cancer Therapy: Potential for Combining CK2 Inhibitors with Various Classes of Cancer Therapeutic Agents 383

Denis Drygin

Introduction 384
Suppression of Apoptosis 385
PI3K-Akt-mTOR Signaling 390
Promotion of Angiogenesis 393
Hsp90 Machinery 395
NF-κB Transcription 399
Wnt Signaling 402
Epithelial-Mesenchymal Transition 405
DNA Damage Repair 405
Other Pathways 409
Concluding Remarks 411
Acknowledgments 411

APPENDIX: CK2 AND ITS FALSE SISTERS: THE RECENT SOLUTION OF A VERY “COLD CASE” 440

INDEX 442

Color plate located between pages 204 and 205.