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Regulators, Targets, and
Clinical Applications

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Edited by

Valerie W. Hu

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PREFACE

Interest in the cell cycle has grown explosively in recent years as a result of the identification of key cell cycle regulators and their substrates. Aside from enhancing our understanding of normal cellular growth controls, this new knowledge has also been valuable in elucidating mechanisms of growth deregulation which occur in diseased states, such as cancer and, in some instances, viral or parasitic infections.

The Thirteenth Washington International Spring Symposium was organized with the intention of bringing together scientists working on different aspects of the cell cycle. Scientific topics presented ranged from molecular regulators and effectors to mitosis-specific changes in cell architecture to the role of the cell cycle in development and disease. The goal of this gathering was to help formulate a more comprehensive and integrated picture of events driving and being driven by the cell cycle, as well as to evaluate the possibilities for clinical application of this knowledge. This symposium, held in Washington, D.C. from May 10-14, 1993, was attended by more than 400 scientists from 20 countries, including many of the scientific leaders in this field. This volume contains most of the papers presented at the seven plenary sessions in addition to selected contributions from a total of nine special oral and poster sessions.

The book is divided into seven sections which are reflective of the seven plenary sessions. Part I focusses on the regulators of the cell cycle and opens with the keynote address presented by Dr. James Maller, co-recipient along with Dr. Tim Hunt of the 1993 Abraham White Distinguished Scientist Award. Drs. Maller and Hunt were honored at the symposium for their significant contributions to the advancement of cell cycle research. In his keynote address, Dr. Maller discussed highlights of studies on oocyte maturation, the resolution of questions raised by these studies, and new questions which have arisen from recent findings, including auto-amplification of MPF. Other papers in this section expand upon the role of protein phosphatases and the D-type G1 cyclins in cell cycle progression.

Part II is concerned with control of cell proliferation and the regulatory mechanisms for entry into and exit from the cell cycle. The chapter begins with a discussion of ERKs, protein kinases which are involved in numerous signal transduction pathways, including transition of cells from G_0 to G_1 . The association of statin with the non-proliferating states of cells, specifically G_0 and cellular senescence, is also described along with a proposed model for the role of statin in the hypophosphorylation of Rb in both these states. Cell senescence is further characterized as a programmed event in which multiple senescence genes are activated and the expression of other genes, such as *cdk2* and cyclins A and B, altered. The ability of DNA tumor viruses to trick a quiescent cell into entering S-phase in order to replicate viral DNA is also described and the roles of Rb and E2F are discussed in this context. In the final two papers of this section, a link between a GTPase cycle and the cell cycle is proposed and the novel idea of a sphingolipid cycle is advanced as a component of the signal transduction pathway regulating cell growth.

In part III, the cell cycle-dependent regulation of gene expression and repair is discussed. Several papers in this section describe the role of both cis- and trans-acting elements in driving transcription at the G₁/S border while others address mechanisms for sensing DNA damage and incomplete DNA replication. A novel method for detecting preferential repair of genes is also described.

Papers in Part IV deal with the regulation of cell entry into M-phase and the associated changes in cell architecture which must occur in preparation for cell division. The roles of the nim 1/cdr 1 kinase and p65 phosphatase as mitotic inducers are described and mitosis-specific changes in protein structure and localization as well as nuclear envelope assembly are discussed.

Perhaps the least developed area in cell cycle research concerns the involvement of cell cycle regulation in development. Part V contains papers that describe the evolution and control of the cell cycle at two levels of development: that of cellular aging and senescence and that of organismic aging and development. Within these contexts, the role of *mos*, G1 cyclins, and heat shock proteins are discussed and the significance of cell proliferation indices with respect to biological aging is addressed. The chapter closes with a discussion of apoptosis and its inverse relationship to cell proliferation.

Parts VI and VII focus on cell cycle regulation and deregulation in disease and explore clinical strategies involving cell cycle arrest or intervention. The aberrant expression of cyclin (E, D₁, A, B) genes in cancer cells is a recurrent theme in these papers, as is the down-regulation of tumor suppressor genes. In one study uniting the two themes, the increased expression of p34^{cdc2} and cyclin A in leukemic cells is suggested to be related to deficient transcriptional regulation by Rb and p53, respectively. The respective roles of genetic damage, faulty DNA repair, and apoptosis are also discussed in relation to carcinogenesis. The last paper in Part VI describes a mechanism for HIV-induced T cell death involving apoptosis following G₂/M arrest, possibly as a result of hyperphosphorylation of p34^{cdc2}.

The involvement of the cell cycle in drug-induced apoptosis is further considered in Part VII and a case is made for altered pH regulation as an important component in this process. In terms of a therapeutic strategy, the importance of determining the molecular basis of specific tumors is stressed in order to utilize approaches based on challenging the defective cell cycle checkpoint in that given tumor. An alternative strategy would be to employ multiple checkpoint override to elicit inappropriate cell cycle progression, and subsequently apoptosis, in tumor cells. Yet another therapeutic approach might be to utilize protease inhibitors to block cyclin degradation leading, in some cases, to catastrophic mitosis. Along another vein, delayed cyclin B expression has been associated with the mechanism for the radioresistance of some tumor cells. Finally, the use of cell cycle analysis by single cell DNA cytophotometry as a prognostic tool for transitional cell carcinomas of the renal pelvis and ureter is described.

The articles in this volume highlight the multidisciplinary nature of current research on the cell cycle and brings together topics that sometimes are excluded from a meeting on cell cycle regulation, such as those related to cellular senescence, development, cell architecture, and clinical applications. This volume should thus be of interest to biochemists, cell, molecular, and developmental biologists, oncologists, pharmacologists, as well as other scientists interested in the regulation of cell proliferation.

Valerie W. Hu

Washington, D.C.

CONTENTS

PART I - REGULATORS OF THE CELL CYCLE

1. Protein Phosphorylation and the Regulation of Key Events in Oocyte and Egg Cell Cycles (**Keynote Address**) 3
James L. Maller
2. Control of G1 Progression by Mammalian D-Type Cyclins 17
Charles J. Sherr*, Hitoshi Matsushime, Jun-ya Kato, Dawn E. Quelle, and Martine F. Roussel
3. Phosphorylation in the Regulation of Protein Phosphatases 25
David L. Brautigan*,¹Jian Chen, Fran Pinault, Jeremy Somers, and Richard Zimmerman
4. Positive and Negative Regulation of Cell Cycle Progression by Serine/Threonine Protein Phosphatases 33
Arthur S. Alberts and Axel Schönthal*
5. Effects of Phosphatase Inhibitors on Mammalian p34^{cdc2} Kinase Activities 41
Xiao-Wen Guo*, John P.H. Th'ng, Richard A. Swank, and E. Morton Bradbury
6. The Meiotic Role of *twine*, a *Drosophila* Homologue of *cdc25* 51
Luke Alphey*, Helen White-Cooper, and David Glover

PART II - CONTROL OF CELL PROLIFERATION

7. Extracellular Signal-Regulated Protein Kinases (ERKS) 1, 2, and 3 61
David J. Robbins, Erzhen Zhen, Mangeng Cheng, Collen A. Vanderbilt, Douglas Ebert, Clark Garcia, Alphonsus Dang, and Melanie H. Cobb*
8. Cell Cycle Traverse and Growth Arrest Control in Senescent Human Fibroblasts 67
Eugenia Wang* and Menq-Jer Lee

9.	Cellular Senescence and the Cell Cycle	79
	Carl Barrett* and Cynthia A. Afshari	
10.	Cell Cycle Targets of Viral Oncoproteins	91
	Joseph R. Nevins	
11.	A GTPase Cycle Coupled to the Cell Cycle	99
	Elias Coutavas*, Mindong Ren, Joel D. Oppenheim, Vijay Yajnik, Peter D'Eustachio, and Mark G. Rush	
12.	Sphingolipids Metabolites: A New Class of Second Messengers in the Regulation of Cell Growth	111
	Sarah Spiegel	

PART III - CELL CYCLE CONTROL OF GENE EXPRESSION AND REPAIR

13.	Histone Gene Transcription During the Cell Cycle	123
	Franca LaBella, Rosanna Martinelli, Neil Segil, and Nathaniel Heintz*	
14.	G1-S Regulatory Promoter Elements and Their Interacting Transcription Factors	127
	Gregory S. Naeve, Li-jing Li, Lin Guo, Ajay Sharma, and Amy S. Lee*	
15.	Regulation of Thymidylate Synthase Gene Expression in Growth- Stimulated Cells	141
	Lee F. Johnson	
16.	The Role of the Transcription Factor E2F in the Growth Regulation of DHFR	149
	Jill E. Slansky* and Peggy J. Farnham	
17.	Activation of the Heat Shock Transcription Factor During G ₁	155
	Jacqueline L. Bruce, Brendan D. Prince, and Stuart K. Calderwood*	
18.	DNA Damage and Cell Cycle Regulation in <i>S. Cerevisiae</i>	163
	Stephen J. Elledge*, Zheng Zhou, James B. Allen, Tony A. Navas, and William J. Jones	
19.	Preferential Repair of Cisplatin Adducts in the Human DHFR Gene During G ₁ Phase Assayed with T4 DNA Polymerase	167
	Nicholas J. Rampino* and Vilhelm A. Bohr	

PART IV - MITOSIS: INDUCTION AND MECHANICS

20.	Direct Inhibition of p107 ^{WEE1} by the NIM 1/CDR 1 Kinase	175
	Laura L. Parker, Sarah A. Walter, and Helen Piwnica-Worms*	

21.	A Human Phosphotyrosine Phosphatase Associated with M phase-Promoting Factor	185
	Robert A. Schlegel	
22.	The Localisation of Human Cyclins and CDKs in the Cell Cycle	189
	Jonathon Pines	
23.	Regulation of Nuclear Envelope Assembly and Disassembly by ARF and Other GTP-Binding Proteins	197
	Annette L. Boman, Kathleen M.C. Sullivan, and Katherine L. Wilson*	
24.	Possible Role of the Multi-Catalytic Proteinase (Proteasome) in Regulating of the Cell Cycle	203
	A. Amsterdam*, F. Pitzer, U. Santarius, A. Dantes, and W. Baumeister	
25.	Cytostellin: A Nuclear Protein That Redistributes to Peripheral Cytoskeletal Locations During Mitosis and G ₁	211
	Stephen L. Warren*, David B. Bregman, Yi Li, and Lei Du	
26.	Evidence for M-phase-Specific Modification of a Gap Junction Protein	223
	Han-qing Xie* and Valerie W. Hu	
27.	Analysis of Centrosome Replication Events in Mammalian Cells	229
	Ron Balczon*, Liming Bao, Warren E. Zimmer, Kevin Brown, Raymond P. Zinkowski, and B.R. Brinkley	
28.	Requirements for Microtubule Polymerization and a Calcium Surge for the Metaphase-to-Interphase Transition in Mature Mouse Oocytes	237
	Ruth M. Moses* and Yoshio Masui	

PART V - CELL CYCLE REGULATION IN DEVELOPMENT

29.	<u>Mos</u> Proto-Oncogene and Cell Cycle Regulation	247
	George F. Vande Woude*, Taesaeng Choi, Renping Zhou, Monica Murakami, Wayne Matten, and Kenji Fukasawa	
30.	Altered Regulation of Cell Cycle Genes and Proteins in Senescent Human Diploid Fibroblasts	251
	Gretchen H. Stein*, Linda F. Drullinger, Emma Lees, Steven I. Reed, and Vjekoslav Dulić	
31.	Cell Proliferation as a Biomarker of Age and Development	263
	M.H. Lu*, S.F. Ali, D.S. He, A. Turturro, and R.W. Hart	
32.	Heat Shock Genes and Cell Cycle Regulation During Early Mammalian Development	271
	David Walsh*, Li Zhe, Frank Zeng, Wu Yan, and Karen Li	

33.	Expression of G1 Cyclins During Early Development of Zebrafish Embryos	283
	Anat Yarden*, Zvi Kam, and Benjamin Geiger	
34.	Apoptosis: Definition, Roles and Regulation	291
	L.E. Gerschenson*, R.J. Rotello, R. Lieberman, and C.-I. Sze	

PART VI - ROLE OF THE CELL CYCLE IN DISEASE

35.	Molecules of Deregulated Cell Cycle Control in Cancer	303
	Arthur B. Pardee*, Qing-Ping Dou, and Khandan Keyomarsi	
36.	The Two Amino Terminal Transforming Functions of the SV40 Large T-Antigen Are Required to Overcome P53-Mediated Growth Arrest	311
	Robin S. Quartin and Arnold J. Levine*	
37.	Down-Regulation of Candidate Tumor Suppressor Genes in Breast Cancer	319
	Zhiqiang Zou, Anthony Anisowicz, Kristina Rafidi, and Ruth Sager*	
38.	Expression and Regulation of Cyclin Genes in Breast Cancer Cells	323
	Elizabeth A. Musgrove*, Michael F. Buckley, Anna deFazio, Colin K.W. Watts, and Robert L. Sutherland	
39.	Genotoxin-Induced Apoptosis: Implications for Carcinogenesis	331
	Steven R. Patierno*, Lori J. Blankenship, John P. Wise, Jian Xu, Laura C. Bridgewater, and Francis C.R. Manning	
40.	Monitoring and Repair of DNA Damage During G ₂ in Relation to Carcinogenesis	341
	Katherine K. Sanford* and Ram Parshad	
41.	Cell Cycle Regulation in Normal Versus Leukemic T Cells	347
	Toshio Nikaido*, Koji Ono, Masuji Yamamoto, Toshiyuki Sakai, and Yasushi Magami	
42.	Cells Undergoing HIV Envelope-Mediated Programmed Degeneration Accumulate in G2/M Phase	359
	Huan Tian, Dan Hartmann, Larry Wahl, Eileen Donoghue, Clare McGowan, Jeffrey Cossman, Paul Russell, Lawrence Samelson, and David I. Cohen*	

PART VII - CLINICAL APPLICATIONS

43.	The Involvement of the Cell Cycle in Apoptosis	369
	Alan Eastman*, Michael A. Barry, and Catherine Demarcq	

44.	Cell Cycle Regulation and the Chemosensitivity of Cancer Cells Kurt W. Kohn*, Patrick M. O'Connor, and Joany Jackman	379
45.	Multiple Cell Cycle Checkpoint Override and Its Potential for Binary Tumor Therapy Robert L. Margolis* and Paul R. Andreassen	389
46.	Radiation-Induced G2 Delay and Mitotic Cyclin Expression W. Gillies McKenna* and Ruth J. Muschel	397
47.	Cyclin B Degradation as a Target of Antiproliferative Drug Action Steven W. Sherwood*, Robert D. Simoni, and Robert T. Schimke	405
48.	Clinical Relevance of DNA Ploidy and Cell Cycle Phases in Transitional Cell Carcinoma of the Renal Pelvis and Ureter: A Study by Means of Static DNA-Cytophotometry Hussain-Al-Abadi* and Reinhard Nagel	411
	Index	421

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