The Cell Cycle

Regulators, Targets, and Clinical Applications

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Edited by
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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 G_1/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, D_1, 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 G_2/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.

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*Presenting Authors at the 1993 Washington International Spring Symposium