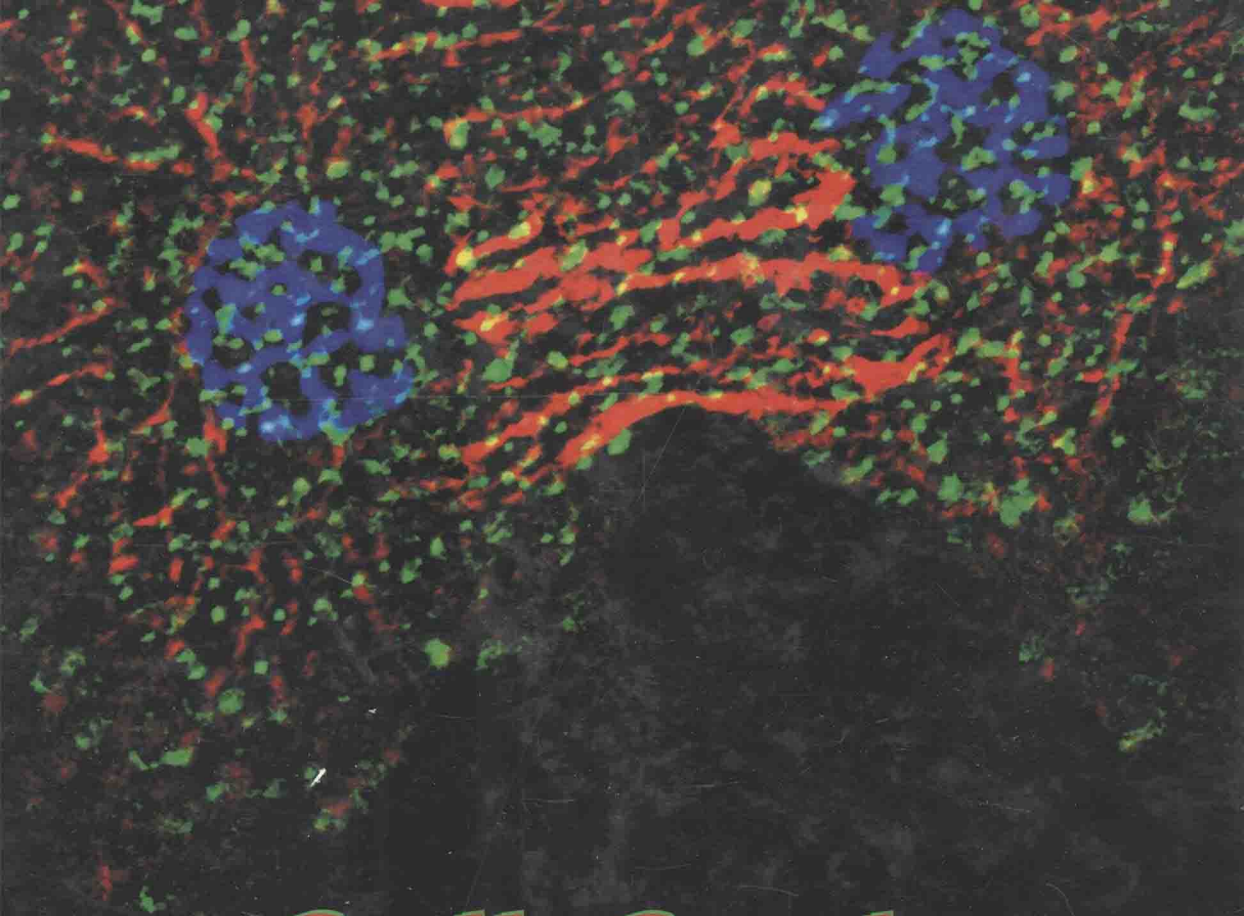

Cell Cycle and Growth Control

BIOMOLECULAR REGULATION AND CANCER

SECOND EDITION

CELL CYCLE AND GROWTH CONTROL

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WILEY-LISS

A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey.
Published simultaneously in Canada.

Library of Congress Cataloging-in-Publication Data:

Cell cycle and growth control: biomolecular regulation and cancer / edited by Gary S. Stein, Arthur B. Pardee.—2nd ed.
p. ; cm.
Rev. ed. of: The molecular basis of cell cycle and growth control. c1999.
Includes bibliographical references and index.
ISBN 0-471-25071-6 (alk. paper : cloth)
1. Cell cycle. 2. Cellular control mechanisms. 3. Cellular signal transduction. 4. Cell differentiation—Molecular aspects.
[DNLM: 1. Cell Cycle—physiology. 2. Cell Death—physiology. 3. Mutagenesis—physiology. QH 604 C3925 2004] I. Stein, Gary S. II. Pardee, Arthur B. (Arthur Beck), 1921— III. Molecular basis of cell cycle and growth control.
QH604 .M6 2004
571.8′4—dc22 2003024668

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

CELL CYCLE AND GROWTH CONTROL

This volume is dedicated to Dr. Arthur B. Pardee in recognition of his seminal contributions to understanding gene regulation and growth control. His pioneering studies in mammalian cells have provided the underlying principles and experimental approaches that are the foundation for our current understanding of growth control and cell cycle progression.

Dr. Pardee is responsible for establishing a restriction point during the prereplicative phase of the mammalian cell cycle and demonstrating its role as a determinant for regulatory mechanisms requisite for the onset of DNA replication. Over the past several years, the Pardee Laboratory has defined interrelationships between the DNA replication cycle and the mitotic cycle, elucidating important differences between normal and tumor cells. His development of differential display technology has led to the identification of genes aberrantly expressed in cancer, as well as broader applications to genes supporting critical regulatory events. He has then translated these fundamental discoveries, exploiting the vulnerability of transformed and tumor cells to biochemical perturbants and the preferential utilization of signaling pathways in tumors to develop novel approaches to cancer chemotherapy.

The profound biological and clinical importance of Dr. Pardee's characterization of regulatory mechanisms that control cell proliferation is reflective of the highest standards of scientific pursuit. In addition to his consistently outstanding research contributions, he has been an inspirational mentor and valued colleague to all of us in the growth control field.

–The Contributors
February 17, 2003

PREFACE

Cell cycle and growth control are profoundly relevant to biological regulation of development and tissue renewal. Equally significant is the recognition that aberrations in mechanisms governing proliferation are linked to the onset and progression of tumorogenesis. From an historical perspective, the foundation for our current understanding of cell cycle and growth control has been systematically constructed during the past fifty years through the combined application of cellular, biochemical, molecular and *in vivo* genetic approaches. The discovery that DNA replication and mitotic division are confined to discrete periods, each preceded and followed by complex and interdependent regulatory events that establish competency for proliferation and cell cycle progression, provided a conceptual underpinning for mechanisms mediating growth control.

Initially, somatic cell fusion and nuclear transplantation studies, together with the selective use of growth factors and inhibitors of macromolecular biosynthesis established fundamental parameters of cell cycle regulation. These key elements of cell cycle control include requirements for transcription to initiate DNA replication and mitotic division as well as the restriction point late in G1 when the threshold for growth factor-independent progression to S-phase is traversed. A persuasive platform for assembling the regulatory cascades that control the cell cycle then evolved by exploiting the power of yeast genetics and subsequent validation in mammalian cells and *in vivo* animal models. Valuable insight was attained into checkpoints and surveillance mechanisms that monitor fidelity of growth control and responsiveness of cells to intra- and extracellular physiological cues. With enhanced capabilities to investigate gene expression through genomic and proteomic approaches, we are becoming increasingly aware of compromises in gene expression that account for breaches in fidelity of cell cycle control in transformed and tumor cells. Significance of the delicate balance between cell survival and default to apoptosis is emerging as a fundamental component of biological control and as a viable therapeutic target.

This book was developed with the objective of presenting concepts, experimental strategies and key findings that enhance understanding of cell cycle and growth control as obligatory physiological processes and from the perspective of compromises that occur in cancer. The first two chapters present an overview of the elegantly organized and stringently orchestrated molecular events that determine cell fate within a context of options for proliferation, differentiation and apoptosis. The perspectives of regulation and structure are explored as a basis for addressing the combinatorial assembly and activity of regulatory complexes that are responsive to integrated cascades of signals that connect molecules with phenotypes. Here, intranuclear trafficking is presented as a mechanism to direct regulatory proteins to the right place at the right time for focal assembly of macromolecular complexes

that support replication, transcription and repair in nuclear microenvironments. The dynamics of regulatory machinery organization is emphasized in relation to temporal-spatial parameters of cell cycle control.

The chapters that follow expand on the organization of cellular events that incorporate a broad spectrum of catalytic and regulatory proteins, not as a comprehensive catalogue, but as a basis for assembling a blueprint for structure-function interrelationships.

Regulatory cascades are dissected to explain the requirements for passage through the G1, S, G2 and mitotic periods of the cell cycle. There is emphasis on positive and negative control that is required for mitotic events that include the regulated as well as the regulatory activities of centrosomes and the mitotic apparatus. Here, implications for chromosome segregation and factors contributing to chromosome instability and aneuploidy are discussed. S-phase regulatory events are examined with emphasis on the coupling of DNA synthesis with histone gene expression and chromatin remodeling. Subtleties of signaling that discriminate between decisions to progress through the cell cycle or default to apoptosis are reviewed. Consideration is not confined to transcription but extends to regulatory events that impact on translational control during the cell cycle. Here, the common denominator is a necessity to balance and selectively amplify or dampen the multidirectional flow of signals that impact on phenotype-specific control of proliferation. This concept is expanded upon in the chapters that are dedicated to regulation of angiogenesis and metamorphosis. Mechanisms that are central to transformation and tumorigenesis are directly examined in four chapters that address DNA repair, oncogenes, and tumor suppressor genes. Emphasis is on cellular compensation and the decision for survival or default to apoptosis. Genomic instability is considered as a function of telomere structure and function and as a consequence of SV40 immortalization. The implications for apoptotic signaling are evaluated on the basis of responsiveness in normal and cancer cells. A central theme is the boundaries between physiological control and a refractory response to checkpoint signals that sustains incurred genomic damage.

The concluding chapters provide an overview of new dimensions to cancer therapy that are based on regulatory parameters of cell cycle and growth control. Options for therapeutic strategies that selectively target components of signaling pathways that mediate steps in establishing competency for proliferation are presented. The complexities of regulatory cascades controlling cell proliferation, differentiation and apoptosis are expanding appreciation for subtleties of growth control and determinacy of cell fate. Each regulatory parameter is a functional component of biological control that enables cells to respond to a broad spectrum of physiological cues. All perturbations in regulatory mechanisms that occur in tumor cells reflect modifications that are consequential for cell fate and cell survival, proliferation, differentiation, senescence, migration and programmed cell death. And, it is becoming increasingly evident that collectively, the insight we are obtaining into regulatory mechanisms operative in normal and tumor cells will facilitate diagnosis of cancer and the ability to treat the disease by selectively targeting molecular signals that exchange regulatory information between the genome and the extracellular environment.

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CONTENTS

PART I

CHAPTER 1

CELL FATES

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Cells develop phenotypes that are determined by organized and regulated molecular processes. Then diverse fates include proliferation, differentiation, and apoptosis. They proceed along several pathways of molecular signaling that are initiated by external factors, which activate cascades of kinases that bring these signals to the nucleus where they initiate transcriptions. These processes require an organized series of cellular and events in which numerous catalytic and regulatory proteins are involved, which in this book are discussed in detail.

PURPOSE AND ORGANIZATION OF THIS BOOK

A living cell can proceed along alternative pathways to a variety of destinations. These include proliferation to form two daughter cells, irreversible or reversible growth arrest, differentiation to a new type of cell as in development or metamorphosis, and death by necrosis or by programmed cell death (apoptosis). At any time the net number of cells is the result of a balance between proliferation and death. These cell fates may be changed in diseases such as the increased growth and decreased apoptotic death of cancer cells. And also they can be modified by drugs and other extracellular agents.

The purpose of this book is to summarize what has been learned about structural, biochemical, and molecular biological events that are the basis for these cell biological processes and their regulations. The emphasis is on vertebrate cells. Thousands of molecules and reactions have already been reported and organized into functional patterns that connect molecules with phenotypes (Fig. 1.1). In this and the next chapter are provided general concepts and underlying principles of regulation and structure. In the other chapters of this book are presented the mass of information, with references and illustrative examples.

Cell Cycle and Growth Control: Biomolecular Regulation and Cancer, Second Edition, Edited by Gary S. Stein and Arthur B. Pardee
ISBN 0-471-25071-6

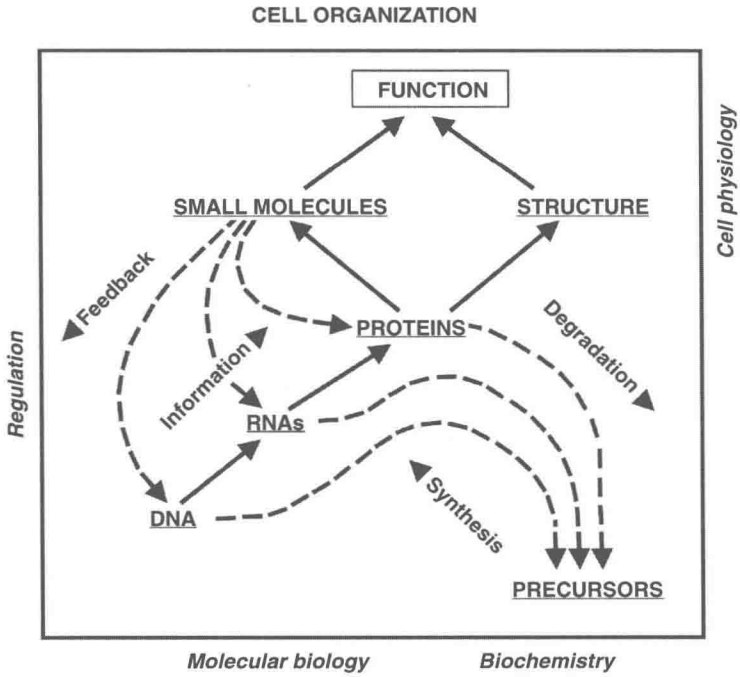

Figure 1.1. Cell molecular and information transfer. The central path of information flow from DNA to cell functions is regulated by feedbacks, indicated on the left. Syntheses from precursors are counterbalanced by degradations, as indicated on the right.

CELL CYCLE BIOLOGY

As an example of a cell fate pathway we outline the general organization of the cell cycle and its biology and biochemistry. By this orderly process one cell grows into two. It is fundamental for the organism's growth and for replacement of cells lost during normal wear and tear (Murray, 1993). Cells from a mature eukaryotic organism can require an interval of a day or more between successive divisions in tissue culture. During this time duplications of all of the myriad molecules that comprise each cell are required, at different times throughout the cycle. The most evident is duplication of deoxyribonucleic acid (DNA), the heredity-carrying material in chromosomes. DNA does not duplicate continously, but only during several hours in midcycle, a period named the S phase for (DNA) synthesis. The cycle is organized, for simplicity, into a sequence of only four major biological and biochemical events which are grouped as gap 1 (G_1 phase) during which a cell prepares for DNA synthesis, DNA synthesis (S phase), preparation for mitosis (G_2 phase), and mitosis (M phase), after which the cell divides and the cycles of the two new cells can commence. For a historical summary, see Baserga (1985).

Quiescence

Most cells in vivo are performing their specialized functions in support of the whole organism. They are quiescent (in G_0 phase), not usually progressing through the cycle, and divide very infrequently. Some cells can remain quiescent for a limited time, an example being fibroblasts whose proliferation resumes after wounding upon stimulation by platelet growth factors. Others such as nerve and muscle cells have become permanently quiescent. Quiescent cells have left the cycle during G_1, and so they contain the unduplicated quantity of DNA, as do G_1 cells. But they differ from G_1 cells in many other properties; in particular, they lack the regulatory molecules required for growth. KI-67 protein is a marker for distinguishing proliferating G_1 from G_0 cells.

G1 Phase

Quiescent cells are activated to proliferate by providing suitable conditions. Nutrients including sugars, salts, vitamins, and essential amino acids are needed for their growth (Baserga, 1985). Normal (nontumor) cells also require epidermal growth factor (EGF), insulin-like growth factor (IGF-1), and transferrin. In an organism growth factors and nutrients must be supplied from blood. For cells to grow in tissue culture, a nutrient medium is required that supplies growth factors usually from added serum. Cells again become quiescent if growth factors are removed. These proteins are required to overcome inhibitions created by contacts between receptors on the cell surface with proteins present in the medium such as growth-negative factor TGF-β, in the extracellular matrix, and on other cells with which a cell is in contact at high density.

Cells increase in size in G_1 phase, but they do not exhibit dramatic changes in morphology. But many molecules are synthesized, and molecular processes take place successively during this interval (see below). The time that cells in culture spend traversing this phase is highly variable, for example, from 6 to 24 hours, unlike the rather uniform times they spend in each of the other phases. G_1 culminates in initiation of DNA synthesis. Growth factors initiate a multiple-step cascade of signals that ultimately activate genes to produce messenger ribonucleic acids (mRNA) and proteins.

S Phase

The requirements of growth factors for passage through G_1 phase are lost at the restriction point (R), located shortly before cells start to synthesize DNA (Pardee, 1989). Progression through later phases of the cell cycle depends on internally generated signals. During the 6 to 8 hours of S phase the nuclear DNA comprising possibly 50,000 genes that are located on 23 pairs of chromosomes is replicated. Each gene is duplicated at a definite time. For example, the dihydrofolate reductase gene that is required for synthesis of DNA is replicated in very early S phase.