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OVERVIEW

Cell Cycle and Growth Control

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Increments in our understanding of eukaryotic cell cycle and growth control have accrued steadily during the past several decades. Landmark contributions initially involved subdivision of the cell cycle into four discrete periods—G_1 (postmitotic presynthetic), S-phase (DNA replication), G_2 (postsynthetic premitotic), and mitotic. Also early on, the requirements of transcription and translation for the onset of DNA replication and mitotic division were established by elegant studies using inhibitors of RNA and protein synthesis. The identification of growth factors and growth factor receptors that mediate competency for proliferation and progression through the cell cycle past a G_1 restriction point provided the basis for pursuit of proliferation-related regulatory mechanisms from both conceptual and experimental standpoints. The identification of proteins that exhibit activity which is preferentially or completely restricted to specific periods of the cell cycle and the characterization of the genes encoding these cell cycle-regulated proteins have been instrumental in focusing on defined components of control mechanisms operative during proliferation. It was the identification and characterization of a series of cell cycle mutants in yeast which yielded valuable insight into growth regulatory proteins and factors that modulate activities of these cell cycle regulatory molecules (e.g., cyclins and cyclin-related kinases). Equally important for our understanding of cell cycle regulatory mechanisms has been increased awareness of the multiple roles of oncogenes and tumor suppressors, many of which encode growth factors, growth factor receptors or molecules which mediate growth factor activity.

The past several years have been catalytic. We are beginning to unravel the complexity of signaling mechanisms which integrate and coordinate transcriptional and post transcriptional control of gene expression requisite for proliferation. We are rapidly expanding our understanding of growth factor-mediated signal transduction pathways which selectively direct and amplify regulatory signals from the plasma membrane to gene promoter regulatory elements where oncogene and steroid hormone control of proliferation occurs. Particularly significant is the realization that promoters of cell cycle-regulated genes are modularly organized and responsive to a broad spectrum of physiological mediators of growth control.

The challenges are formidable and include the following: Mechanisms by which the combined activities at independent promoter elements are integrated to support responsiveness to both positive and negative growth regulatory signals are being pursued. Coordinate control of genes functionally related to components of cell cycle and/or growth regulation is being investigated. Interrelationships between cell structure and gene expression are expanding our understanding of in vivo regulatory parameters operative for growth control in cells and tissues. The complex and dynamic protein-protein interactions which are involved with growth control and cell cycle progression at the transcriptional and posttranscriptional levels are only beginning to unfold.

This prospect series on "Cell Cycle and Growth Control" cannot be inclusive. Rather it focuses on several representative examples of fundamental concepts and experimental approaches which have provided the foundation for ongoing pursuit of cell cycle-associated gene regulatory mechanisms. The article by Pardee (page 375, this issue) functionally defines cell cycle and growth control from the perspective of a series of regulatory mechanisms supported by control of gene expression at multiple levels. This theme is expanded upon in the prospect by G. Prem Veer Reddy (page 379, this issue) in which calcium-mediated regulatory events at the G_1/S-phase transition point are discussed as well as in

the prospect by Lee F. Johnson (page 387, this issue) where significance of posttranscriptional regulation of thymidylate synthase is emphasized and in the Stein et al. (page 393, this issue) prospect where the principal focus is transcriptional control of cell cycle regulated gene expression. The Soprano (page 405, this issue) article provides valuable insight into model systems for investigating cell cycle and growth regulatory mechanisms. Johnson et al. (page 415, this issue) cover G protein-mediated mitotic signaling mechanisms. Both the Doenecke et al. (page 423, this issue) and Stein et al. (page 393, this issue) prospects address structure-function interrelationships which may contribute to proliferation-related transcriptional regulatory mechanisms. The subject of the Wang et al. article is senescence-related programmed cell death (page 432, this issue). The prospect series is concluded with a presentation by Kohn et al. (page 440, this issue) of expectations for new opportunities where knowledge of cell cycle regulatory events and growth regulatory molecules can be applied to cancer therapy.