Version 2.0

Abstract

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Grant Number:	1R01CA077245-01
PI Name:	DYNLACHT, BRIAN D.
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PI Title:	ASSOCIATE PROFESSOR
Project Title:	TRANSCRIPTIONAL REGULATION BY THE PRB PROTEIN FAMILY

Abstract: This proposal investigates the mechanisms by which the retinoblastoma tumor suppressor protein (pRB) and two related proteins, p107 and p130, modulate transcription. The pRB family plays an important role in restraining cell proliferation, and mutations of pRB have been found in a variety of cancers. It is thought that these proteins suppress growth in part through an ability to regulate transcriptional activity of proteins to which they bind. We propose a biochemical approach toward studying the function of the pRB family of proteins. Our objectives include the following: (1) determining whether the pRB family targets proteins in the basal transcription machinery; (2) understanding how pRB can inhibit and activate transcription; and (3) understanding how the pRB-related proteins, p107 and p130, and p107/p130 complexes with cyclin-dependent kinases, modulate gene expression and growth. Each of these specific aims is part of an overall attempt to understand how certain critical cell cycle regulators modulate transcriptional responses during cell proliferation. These studies will be carried out using a mammalian in vitro transcription system reconstituted with purified basal and sequence- specific transcription factors and recombinant cell cycle proteins. The well-defined nature of these in vitro assays circumvents many of the complications of studying cell cycle-regulated events in vivo. In vivo growth suppression, protein-protein interaction assays, and DNA-binding analyses with purified or partially purified proteins will be used in parallel to confirm and strengthen our in vitro transcription results. Although much research has focused on the regulatory cues that promote cell growth, our understanding of the mechanisms that drive proliferation is still rudimentary. It is clear that a thorough knowledge of the interplay between gene expression and cell cycle regulatory proteins will be of fundamental importance in understanding the mechanisms for cell cycle progression in both normal and cancer cells.

Thesaurus Terms:
cell growth regulation, genetic transcription, retinoblastoma protein, transcription factor DNA binding protein, cell cycle, cell cycle protein, cell proliferation, cyclin dependent kinase, enzyme activity, gene induction /repression, genetic promoter element, intermolecular interaction, neoplastic growth, phosphorylation, protein binding, recombinant protein

cell line, gel mobility shift assay, transfection, western blotting

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Fiscal Year: 1998
Department: MOLECULAR AND CELLULAR BIOLOGY
Project Start: 19-JUN-1998
Project End: 31-MAR-2003
ICD: NATIONAL CANCER INSTITUTE
IRG: MBY