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Abstract

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PI Title:
Project Title: REGULATION OF MITOSIS BY PROTEOLYSIS IN YEAST

Abstract: DESCRIPTION: In all eukaryotes, entry into S phase and mitosis is triggered by protein kinases, whose activity depends on regulatory cyclin subunits (cyclin-dependent kinases; Cdks). Different types of Cdks initiate different events of the cell cycle. It is therefore critically important that their activities are restricted to the appropriate cell cycle stages. Ubiquitin-dependent proteolysis of mitotic cyclins plays a key role in restricting the activity of the mitotic Cdks. Mitotic cyclin proteolysis inactivates mitotic Cdks at the end of mitosis and prevents their accumulation throughout G1. During S phase and early mitosis, mitotic cyclin proteolysis is inhibited, allowing mitotic Cdks to accumulate. The goals of this proposal are: (1) to identify the pathway(s) of activation of mitotic cyclin proteolysis; (2) to determine the role of Cdks in repression of mitotic cyclin proteolysis; and (3) to identify genes required for repression of mitotic cyclin proteolysis during S-phase and early mitosis. To characterize the pathway(s) of activation of proteolysis, genes will be identified specifically defective in this process. These analyses will utilize assays for activation of proteolysis and maintenance of proteolysis, recently developed by Dr. Amon. Using these assays, the putative tyrosine phosphatase Cdc14 has already been identified as being specifically required for activation but dispensable for maintenance of mitotic cyclin proteolysis. The role of CDC14 in activation of mitotic cyclin proteolysis will be characterized in detail. Two approaches will be taken to investigate the role of Cdks in repression of mitotic cyclin proteolysis during S phase and early mitosis. (1) Biochemical experiments will address whether Cdk phosphorylation directly inhibits the proteolysis process. (2) A genetic approach will identify genes required for repression of mitotic cyclin proteolysis during S phase and early mitosis. Uncontrolled cyclin expression can be lethal. It has been linked to cancerous transformation: cyclin overexpression is a prominent feature of certain tumors including breast cancer. Identifying and characterizing the regulatory networks, such as mitotic cyclin proteolysis, that restrict the activity of these proteins will open avenues towards the development of cancer diagnostics and therapeutics.

Thesaurus Terms:
cell cycle, cell growth regulation, cyclin dependent kinase, proteolysis
cell cycle protein, cyclin, enzyme activity, gene expression, gene induction /repression,

phosphorylation, protein tyrosine phosphatase
immunoprecipitation, temperature sensitive mutant, yeast two hybrid system

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