Unconventional cyclin function during cellular growth, differentiation and stress responses

Synopsis: Insight into the cell cycle regulatory proteins that restrict cellular proliferation and promote differentiation is essential for understanding the processes that go awry in neoplastic and developmental diseases. Improved knowledge of these proteins and their mechanisms will further the development of novel therapeutic interventions for these diseases. We are investigating the contributions of the novel "G" family of unconventional cyclins to growth control, with a current emphasis on cyclin G2. Contrasting the prototypical CDK-activating cyclins that are upregulated in proliferating cells and promote cell cycle progression, elevated expression of cyclins G1 and G2 correlates with growth arrest and induces cell cycle arrest in transfected cells. Importantly, the gene encoding cyclin G1 is directly activated by the transcription factor and tumor suppressor p53, whereas the gene encoding cyclin G2 is directly regulated by the stress activated forkhead box O transcription factors FOXO1 and FOXO3a linked to tumor expression. As both cyclins G1 and G2 are evolutionarily conserved from fish to humans, and knock-out of the single cyclin G homolog in Drosophila is embryonic lethal, members of this unique cyclin family likely serve important functions in regulatory pathways that modulate growth and development.

We and others found that cyclin G2 levels are significantly upregulated in cells responding to diverse cell cycle-inhibitory signals (e.g. blockade of growth factor signaling, induction of oxidative and genotoxic stress, cellular differentiation), but downregulated upon induction of pro-growth mitogenic signals (e.g. estrogen, insulin, Shh, IL-4, LPS). Our work showed that ectopically expressed cyclin G2 inhibits CDK2 activity and induces a G1/S-phase cell cycle arrest that requires intact p53. We determined that cyclin G2 is a PP2A and centrosome-associated nucleocytoplasmic shuttling protein that may modulate microtubule stability and regrowth. Emerging studies suggest that repression of cyclin G2 expression promotes cellular growth and replication. Current research projects in the laboratory are focused on defining the regulation and function of cyclin G2 during: 1) cellular responses to therapeutics-induced inhibition of endocrine and growth factor signaling pathways in breast cancers and B cell lymphomas, 2) cellular responses to genotoxic stress and DNA damaging cancer therapeutics, and 3) the differentiation and post-mitotic growth of neurons.

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