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Identifying the Structural and Enzymatic Contributions of Casein Kinase 2 to the Regulation of Ribosome Assembly and Cell Growth

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Background:

The ribosome has recently been directly linked to cancer, as cellular growth rate is dependent on the rate of ribosome biogenesis, and that ribosome assembly defects, termed ribosomopathies, are associated with various cancers, such as in Diamond-Blackfan anemia and myelodysplastic syndrome. In addition, the expression of ribosome assembly factors, and of ribosome assembly itself, is upregulated in many cancers. Thus, ribosome assembly is an emerging interest for chemotherapeutic targeting. The small subunit (SSU) processome, is a large ribonucleoprotein complex responsible for assembly of the small subunit of the ribosome. Protein kinase/Casein kinase 2 (CK2) is a pleotropic and constitutively active serine-threonine kinase complex associated with the SSU processome, and a likely regulatory step in ribosome assembly.

Objective:

The role of CK2 in the SSU processome in ribosome assembly is unknown. Our objective is to identify CK2's role in ribosome assembly, examining both its enzymatic and structural contributions to the regulation of ribosome biogenesis, and as a potential avenue for therapeutic intervention.

Methods:

Sequence alignments were used to identify conserved regions and catalytic residues in the two kinase Cka1 and Cka2 subunits of CK2. Using a yeast model system, wild type and catalytically dead Cka1 and Cka2 clones were created through Gateway cloning and site directed mutagenesis. These were transformed into yeast CK2 Gal depletion strains capable of genetic depletion of the endogenous Cka1 and/or Cka2 proteins

Results:

Using growth curves, an accepted proxy for ribosome assembly, we have shown that overexpression of catalytically dead Cka1 or Cka2 kinase subunits results in reduced cell growth and unexpectedly yields a dominant negative phenotype.

Conclusion:

This implies that catalytically dead CKa1 or Cka2 may unproductively occupy their kinase substrates and sterically or functionally block subsequent ribosome assembly events. Our results will continue to be assessed using northern hybridization analysis of the pre-rRNA processing pathway.