Poster Presentation

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Crystal structures of GCN2 C-terminal domain: Insight into GCN2 regulation

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General control non-derepressible 2 kinase (GCN2) is a serine threonine kinase that curtails translation in response to diverse stress stimuli [1]. It is a primary sensor of amino acid starvation and mediates translation repression by phosphorylating eIF2 [2]. In addition to the kinase domain, GCN2 contains two regulatory regions; a histidyl-tRNA synthetase-like domain (HisRS) and a C-terminal domain (CTD), which function together to sense nutrient depletion. Both domains have been proposed to bind uncharged tRNA's that accumulate during amino acid starvation followed by dimerization of the kinase domain facilitating activation of GCN2 [3]. Thus, while the CTD plays an important regulatory role in activating GCN2, information on how the CTD facilitates dimerization and whether the CTD plays a similar role in murine GCN2 is limited. Moreover, the sequences of vertebrate CTDs share less than 10% sequence identity with their yeast counterpart; therefore, it is not known whether regulatory mechanisms in GCN2 are conserved across different species. We present here the experimentally phased crystal structures of murine CTD at 1.9 Å and yeast CTD at 1.95 Å. Both murine and yeast CTDs share a novel interdigitated dimeric organization, although the dimeric structures differ somewhat in overall shape and size. Additional biochemical analysis of the murine CTD confirms an important role for dimerization in its activation. Moreover, functional studies reveal that both yeast and murine GCN2 have similar nucleic acid binding properties, but mGCN2 does not appear to exhibit ribosomal association, a key feature in the model for regulation of yeast GCN2, suggesting that there are regulatory differences between the murine GCN2 and its yeast counterpart. Our data provides a basis for understanding the role of the CTD in regulation of GCN2 in both yeast and mammals.

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