Structural Basis for Autoinhibition and Activation of eIF2α Protein Kinase GCN2

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The GCN2 protein kinase (PK) couples the rate of protein synthesis to amino acid stores by phosphorylating eukaryotic translation initiation factor 2. The autoinhibited form of the GCN2 PK domain is activated in cells starved of amino acids by binding of uncharged tRNA to a histidyl-tRNA synthetase (HisRS)-like domain. Crystal structures of a GCN2 PK dimer have been determined for wild-type and mutant forms in the apo state and bound to ATP or AMPPNP. These structures reveal that autoinhibition results from stabilization of a closed bi-lobate conformation of the apo protein that restricts ATP binding. A hyperactive mutant form of the enzyme (*R794G*) shows a conformational change in the hinge region connecting the N- and C-lobes and significant intra-domain movement that enhances ATP binding and hydrolysis. We propose that interactions between the PK domain and the tRNA-bound form of the HisRS domain remodel the hinge region in a manner similar to the mechanism of enzyme activation by the *R794G* mutation. A hypothetical structural model of a PK_2HisRS_2 tetramer places the kinase hinge near the PK-HisRS interface, poised for allosteric modulation following uncharged tRNA binding.

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