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Title and Abstract

DYRK protein kinases, a model for co-translational phosphorylation

The phosphorylation of proteins on serine, threonine or tyrosine residues is arguably the most pervasive and important post-translational modification affecting cellular life. The phosphorylation of activation loop residues within the kinase catalytic domain is perhaps the most important mechanism for regulating the catalytic activity of a protein kinase. Members of the DYRK (Dual-specificity tyrosine phosphorylation–regulated kinase) family of protein kinases autophosphorylate a tyrosine residue in their activation loop, an essential maturation event required for full enzyme activity. Once phosphorylated, DYRKs lose tyrosine kinase activity and function as serine/threonine kinases. In contrast to existing models of inter-molecular phosphorylation, we demonstrate that phosphorylation of the DYRK activation loop is intra-molecular, and is mediated by a short-lived transitional intermediate occurring during co-translation of the protein. Through bioinformatics and mutational analyses, we identify a highly conserved domain in the non-catalytic amino-terminus of Class II DYRKs that transiently converts the molecule into an intra-molecular kinase capable of autophosphorylating the activation loop tyrosine. This chaperone-mediated intra-molecular mechanism is conserved in the GSK3 (Glycogen synthase kinase 3) family of protein kinases, and is likely to be widespread in many important protein kinases. The characterization of this mechanism has important ramifications for the design of novel protein kinase inhibitors.