Poster Presentation

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Crystal structure of a mammalian pseudokinase reveals an original dimerization

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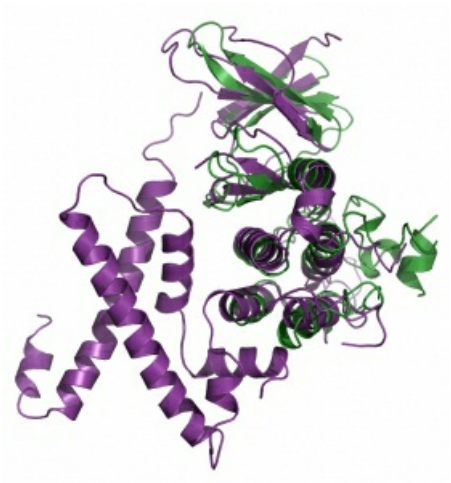
Although partially or totally devoid of any ATP binding or hydrolysis, pseudokinases are now recognized as key players in cell signaling. However, their functioning is still unclear for a number of such pseudokinases encoded in the mammalian genomes. Here we describe the crystal structure of the folded region of a large pseudokinase from rat, that belongs to an extending superfamily of mammalian pseudokinases involved in cancers. We have solved the crystal structure by molecular replacement, at a 3.0 A resolution, despite a low overall sequence identity (20-25% over the whole kinase domain), using the software Phenix, an ensemble of partial models built using our server @TOME-2 and data recorded automatically on the beamline MASSIF-1 at the ESRF synchrotron (unpublished results).

The structure, now refined at 2.8 A resolution, contains a classical protein kinase fold, which is devoid of any ATP-binding activity. Indeed, our structure revealed a particular "inhibitory triad", that is conserved in other members of this superfamily, and holds tightly the putative catalytic lysine to prevent any ATP binding or hydrolysis. Interestingly, the pseudokinase also possesses N- and C-terminal extensions forming an original dimerization domain (unpublished results). Directed mutagenesis is currently being undertaken to address the role of the so-called inhibitory triad and the importance of the dimerization interface.

This pseudokinase and scaffolding protein has been linked to cancer by up-regulating protein tyrosine phosphorylation. Our results suggest a structural model for understanding how this pseudokinase induces protein tyrosine phosphorylation and nuclear transcription.



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