

Structural Investigation of Human PP2A Regulation by Protein Methylation

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Abstract:

Protein serine/threonine phosphatase 2A (PP2A), a conserved protein found in many species, plays an important role in various cellular processes including cell growth, differentiation, signal transduction, DNA replication, transcription, protein synthesis and apoptosis. Deregulation of PP2A methylation is linked to Alzheimer's disease and increased susceptibility to pathogen infections. PP2A was identified as an important tumour suppressor protein and hence a potential target for cancer therapeutic strategies. PP2A comprises a core structure of a 65 kDa scaffolding subunit A and a 36 kDa catalytic subunit C, which associates with a variable regulatory subunit B to form a heterotrimeric holoenzyme. Recently, two different x-ray crystallographic structures of PP2A were determined with the B' (B56-r1/PR61) subunit. Different heterotrimeric compositions influence the enzyme's cellular location and substrate specificity.

Leucine carboxyl methyltransferase 1 (PPM1) and protein phosphatase methylesterase 1 (PME1) are involved in PP2A's methylation and de-methylation respectively. Recent research has demonstrated that methylation of the PP2A C subunit at the carboxyl-terminus, residue Leu309, by PPM1 is essential in facilitating formation of the heterotrimeric PP2A complex. In contrast, PME1 is thought to associate with and stabilize the inactivated form of PP2A complex.

Work presented here aims to determine the crystal structure of PPM1 and PME1, the effect of the putative catalytic residue mutations of PME1, and further research molecular basis of PP2A and PME1/PPM1 interactions.