Structural Insights into the Substrate Binding Mechanism, Inhibition and Regulation of Pim-1

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Pim-1 is a highly conserved cytoplasmic serine/threonine kinase that was first discovered as a preferential proviral insertion site in Moloney Murine Leukemia Virus (MoMuLV) induced T-cell lymphomas. The expression pattern of Pim-1 is widespread and the protein is over-expressed in a series of tumors but highest expression levels are found in cells of the hematopoietic and lymphoid system. Pim-1 phosphorylates a number of signal transduction proteins involved in the regulation of cell cycle, apoptosis, differentiation and proliferation.

We determined the structure of human Pim-1 in complex with an inhibitor of the bisindolyl maleimide (BIM) class as well as in ternary complex with its consensus peptide (pimtide) and BIM-1/AMPPNP that provides interesting insight into the substrate binding and inhibition of Pim-1 and suggests further applications of BIM-like compounds for treatment of leukaemia and other Pim-1 dependent cancer types.

Structural analysis of the monophosphorylated Pim-1 and auto-phosphorylation studies show that the human Pim-1 kinase activity is not influenced by auto-phosphorylation of activation loop residues. The N-terminus of Pim-1 has been shown to be important for several Pim interacting proteins, it is therefore likely that phosphorylation at Ser8 indicated by phosphorylation mapping plays a role in modulating these interactions.

Keywords: kinase structure, phosphorylation, drug design