The Structural Basis for Ser/Thr Protein Phosphatase Inhibition

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Serine/Threonine Protein Phosphatases are important in many cellular processes including glycogen metabolism and immunosuppression. Many marine prokaryotic organisms produce structurally diverse phosphatase inhibitors that can be toxic. The surface of Ser/Thr Phosphatases contain an inhibitor-binding loop which is important in inhibitor activity. How this loop determines inhibitor-specificity is unknown. We have solved the structures of Protein Phosphatase-1 (PP1) bound to four marine natural product inhibitors: okadaic acid, motuporin, clavosine and microcystin-LA(2H)[1]. These inhibitors bind in a similar manner to the phosphatase, exhibiting analogous interactions and showing no structural rearrangement of the inhibitor-binding loop. A structure solved using a mutant PP1, where the inhibitor-binding loop from calcineurin has been substituted for the native loop, reveals repositioning of only specific amino acid side-chains. These results indicate that inhibitor specificity in Ser/Thr Phosphatases is most likely due to specific interactions within the inhibitor-binding loop and not structural rearrangements. There are observable differences in the binding of inhibitors to PP1 and the PP1-calcineurin hybrid, information that may be utilized in the design of new immunosuppressant calcineurin inhibitors.

[1] Maynes J.T., Perreault K.R., Cherney M.M., Luu H.A., James M.N.G., Holmes C.F.B., *J. Biol. Chem.*, 2004, **279**, 43198.

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