Exploring the Interplay of Dynamics and Allosteric Regulation in PTP1B

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Allosteric regulation is a fundamental property of proteins in which an effector modulates the activity of a protein by binding to a surface site far from the protein's active site. Such regulation is both ubiquitous in nature and provides a promising way to control proteins pharmacologically. Key to the latter goal, however, is understanding how the concerted motions of amino acids within the protein propagate changes from allosteric binding sites to the active site. We investigated the concerted motions in the model system protein tyrosine phosphatase 1B (PTP1B), which contains a flexible WPD loop that transitions between open and closed states. We used a combination of computational and experimental approaches to determine the regions of the protein whose motions correlate with the motion of the WPD loop. We analyzed over 350 crystal structures of PTP1B to build a conformational landscape that showed that the WPD loop was coupled to the L16 loop; we also showed that the C- terminal α7 helix was coupled to both these loops. Experimentally, we also solved two novel apo structures of a PTP1B lacking the α7 helix and showed that the α7 helix is required for the WPD loop to sample both open and closed states in a crystal without a substrate analog. These results suggest that the α7 helix acts as a communication pathway between the WPD and L16 loops, offering the L16 loop and α7 helix as promising targets for the design of allosteric inhibitors.

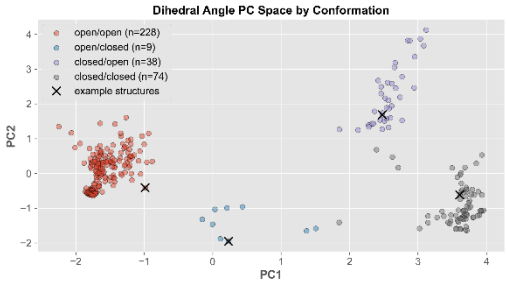

Figure 1

Figure 2

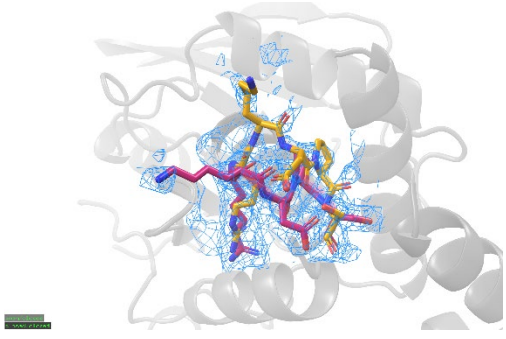

Figure 3