Substrate specificity is a fundamental property of enzyme catalysis. Enzymes are characterized by their exceptional capacity to efficiently catalyze a great number of stereospecific chemical reactions in all organisms. A selective binding and stabilization of the transition state rather than more stable forms of substrates seems to be the major determinant of the chemical reaction step. To achieve such enzyme-transition state complex, a particular spatial arrangement of the active site is required, highlighting the importance of protein dynamics and conformational changes in substrate recognition and catalysis [1]. Specifically, protein conformational changes not only involve local reorganization of flexible loops and side-chain residues, but also, in many cases, domain motions and protein oligomerization events. In addition, as a consequence of protein-protein interactions, post-translational modifications, and non-covalent associations with small-molecule inhibitors or activators, protein dynamics critically modulate enzyme catalysis. Thus, the elucidations of the molecular mechanisms by which these events modulate the function and substrate specificity of enzymes represent a major challenge.

Combining Crystallography with Small-Angle X-ray Scattering (SAXS) can advance our understanding of these dynamic processes. During this talk we will focus on two cases where combining these techniques have proven important. The first, is the phosphatidylinositol mannosyltransferase PimA, an essential membrane-associated enzyme that initiates the biosynthetic pathway of key structural elements and virulence factors of the cell wall in Mycobacterium tuberculosis [2,3]. PimA shows an exceptional flexibility along the catalytic cycle, including β-strand→α-helix and α-helix→β-strand transitions [4]. The second case is the Rv2466c, a key oxidoreductase where the redox state regulates the enzyme conformation, mediating the reductive activation of TP053, a thienopyrimidine derivative that kills replicating and non-replicating M. tuberculosis [5,6].


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