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Selective Covalent Inhibition of "Allosteric Cys121" Distort the Binding of PTP1B Enzyme: A Novel Therapeutic Approach for Cancer Treatment

Covalent inhibition targeting non-catalytic residues is rapidly gaining attention in drug discovery. Protein tyrosine phosphatases 1B (PTP1B) is an attractive target for therapeutic interventions in cancer and other diseases. Two binding sites of PTP1B enzyme were identified, catalytic and allosteric. The catalytic site is deep and narrow which protects the active site amino acid residue Cys215 from covalent inhibition, whereas the allosteric site is more hydrophobic and less conserved with Cys121 residue, to which covalent inhibitors can bind. A recent experimental report highlighted that a highly selective inhibitor, 73U, was found to bind covalently in the allosteric region of PTP1B enzyme. Using a robust covalent simulations protocol which was developed in-house, we previously explored the mechanism of irreversible inhibition in ERK2 kinase as opposed to non-covalent inhibition. Herein, by applying a similar protocol, we further explore the origin and impact of covalent inhibition upon inhibitor binding to allosteric site. For this, covalently-bound and apo enzymes were investigated. Results revealed that allosteric covalent inhibition has ensued in a significant disturbance in the overall network of interaction between Cys121 and other nearby residues, more specifically Tyr124 and His214. The covalent inhibition also exhibited better protein stability as evident from positive correlation between residues in the allosteric site and multiple van der Waal, hydrogen bond and ionic interactions. In the covalent model simulation, surface analysis revealed an increase in the accessible surface area in order to facilitate for the covalent inhibitor to sink in. These findings indicate that exploring allosteric covalent mechanism of PTP1B enzyme offers the opportunity to develop novel PTP1B covalent inhibitors with high potency and selectivity for cancer and other diseases.

Presenter Biography

Shama Khan is pursuing PhD in the field of Pharmaceutical Chemistry in UKZN Westville under the supervision of Prof Soliman. Her topic of interest is Covalent and Non-covalent inhibitory mechanism of drugs in cancer therapy.

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