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Exploring the Structural Mechanism of Covalently Bound E3 Ubiquitin Ligase: Catalytic or Allosteric Inhibition?

Covalent inhibition has recently gained a resurgence of interest in several drug discovery areas. The expansion of this approach is based on evidence elucidating the selectivity and potency of covalent inhibitors when bound to particular amino acids of a biological target. The Nedd4-1, an E3 ubiquitin ligase, is characterized by two covalent binding sites, of which catalytic Cyscat and allosteric Cysallo are enclosed. This enzyme has demonstrated inhibition at both the above-mentioned binding sites; however, a detailed molecular understanding of the structural mechanism of inhibition upon Cyscat and Cysallo binding remains vague. This prompted us to provide the first account of investigating the preferential covalent binding mode and the underlying structural and molecular dynamic implications. Based on the molecular dynamic analyses, it was evident that although both catalytic and allosteric covalent binding led to greater stability of the enzyme, a preferential covalent mechanism of inhibition was seen in the allosteric-targeted system. This was supported by a more favorable binding energy in the allosteric site compared to the catalytic site, in addition to the larger number of residue interactions and stabilizing hydrogen bonds occurring in the allosteric covalent bound complex. The fundamental dynamic analysis presented in this report compliments, as well as adds to previous experimental findings, thus leading to a crucial understanding of the structural mechanism by which Nedd4-1 is inhibited. The findings from this study may assist in the design of more target-specific Nedd4-1 covalent inhibitors exploring the surface-exposed cysteine residues.

Presenter Biography

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