Identifying Key Residues Involved in Allosteric Regulation of Human SIRT1 Deacetylation Activity

SIRT1 is a mammalian NAD\(^+\)-dependent lysine deacetylase involved in the regulation of physiological processes, such as insulin metabolism and neurodegeneration. Small-molecule modulators, such as resveratrol, bind to the N-terminal region to allosterically regulate SIRT1 activity. Understanding the mechanism for this allosteric effect on SIRT1 would provide insights into drug design to modulate SIRT1-dependent deacetylation on specific substrates.\(^1\) The overall goal of this research is to identify key residues that are involved in allosteric activation of the enzyme, also known as an allosteric switch-like region. Using computational methods based on the primary sequence of SIRT1, we identified residues 186-193 to have a propensity to exhibit switch-like behavior,\(^2,3\) and constructed mutants that were predicted to abolish this propensity. To confirm the switch-like predictions, we studied the enzyme kinetics\(^4\) of the wild-type and mutant constructs on a known substrate in the presence and absence of resveratrol. The results of which suggested that the 190-193 region would likely contain a switch-like region. Additional predictions by an improved logistic regression approach pinpointed a possible switch-like residue at 193 within this region. We are currently conducting enzymatic experiments to confirm if residue 193 is indeed a key switch-like residue. The results of this study will provide a novel target site for controlling the regulation of SIRT1 activity as a therapeutic approach.


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