TITLE: Critical roles of Human SIRT3 modulators, from nicotinamide to iso-nicotinamide

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ABSTRACT *(150 words limit)*

Human sirtuin type 3 (hSIRT3), a major mitochondrial protein, has an NAD+ - dependent deacetylase activity regulating the global lysine acetylation. hSIRT3 is associated with human pathologies, such as metabolic syndrome, cancer, and geriatric diseases. The kinetics and mechanism of inhibition of hSIRT3, as well as that of Sir2, were investigated *in vitro* and computationally. Physiological concentrations of nicotinamide competitively inhibit human recombinant hSIRT3 versus NAD+. The critical roles of nicotinamide and its analogue (iso-nicotinamide) as inhibitor/activator of hSIRT3 were discussed as well. Induced fit protein-ligand docking along with a subsequent binding affinity estimation using molecular mechanics /generalized born surface area (MM/GBSA) calculations show that nicotinamide binds approximately equally well to the two alternate binding sites of Sir2, known as the AB or AC pockets, and that nicotinamide preferentially binds to the AC pockets of hSIRT3. These results provide important insights for the development of SIRT3-specific modulators.