DBT-THSTI study paves way for innovative treatment strategies

New Delhi, April 06: Target selectivity is a pivotal aspect in the drug discovery pipeline and certainly a parameter that is not trivial. Researchers at DBT-Translational Health Science and Technology Institute (DBT-THSTI) are working on sirtuins (Sirt1–3), a nicotinamide adenine dinucleotide (NAD+)-dependent epigenetic protein modulators, as these have been the focus of research by researchers and pharmaceutical companies to develop innovative treatment strategies for various pathological conditions such as type II diabetes, neurological disorder, antiaging, and cancer. They are located in distinct cellular compartments and act differently under various pathological conditions, the selective inhibition appears to be a promising strategy for understanding their biological function and for discovering effective therapeutics for various diseases.

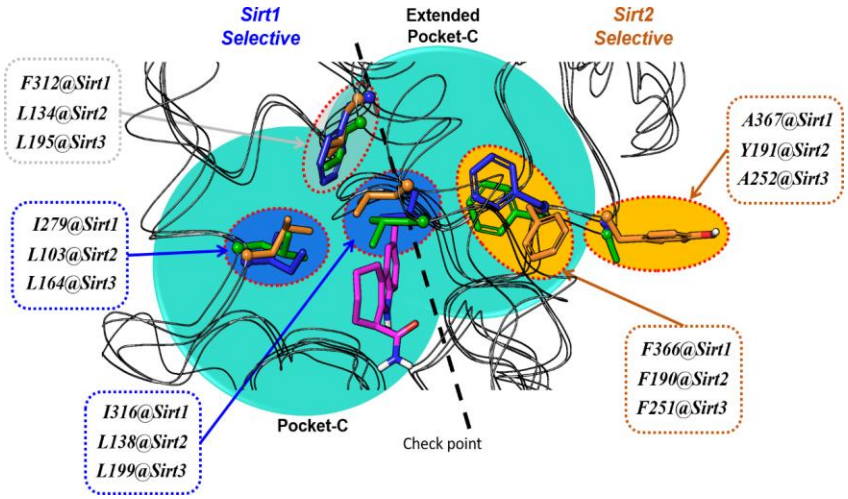

Figure: The residues playing a key role in Sirt1 selectivity are highlighted in blue while those that play a role in extension of binding site formation are highlighted in orange dotted circle.

In the last decade, many structurally diverse small-molecule modulators of Sirt1-3 have been reported. However, due to high amino acid conservation and structural similarity of the catalytic core of Sirt1-3, most of the modulators lack selectivity, potency or pharmacological properties. This turned out to be a reason for their failure in clinical trials, preventing them from entering in the drug development process. This further intensifies the need for the elucidation of the mechanism for selectivity between Sirt1-3.

Since the structural, dynamical architectures and residual positioning are a prerequisite for the structure-guided designing and discovery of selective modulators, therefore, the team of researchers at THSTI used an advanced arsenal of computational protocols to explore the selectivity mechanism. They identified that the binding sites in Sirt1-3 exist in variable shapes and a breathing motion was observed among binding site residues. By using the comparative energetics, residual wiring and mutational studies, the researchers have found that residues I279 and I316 are critical for the Sirt1 selectivity.

Further, they explored that the side-chain reorientation occurred in residue F190 due to non-conserved residue Y191 played a major role in the formation of an extended selectivity pocket in Sirt2. These results will help researchers to understand the mechanism of targets selectivity and how it can be used in designing of selective inhibitors in drug discovery.

Complete paper at https://pubmed.ncbi.nlm.nih.gov/33606530/

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