DBT-THSTI team studies protein-protein interaction for drug designing

New Delhi, Feb 12: The dynamics and plasticity of the PD-1/PD-L1 axis are the bottlenecks for the discovery of small-molecule antagonists to perturb this interaction interface significantly. Understanding protein-protein interaction (PPI) process is significant in structure-based drug designing. Food and Drug Administration (FDA)-approved anti-PD-1 monoclonal antibodies (mAbs) are the first-in-class with distinct binding modes to access this axis clinically; however, their mechanistic aspects still are not very clear.

In a new study, a team from DBT- Translational Health Science and Technology Institute (DBT-THSTI), Faridabad and Delhi Pharmaceutical Sciences and Research University (DPSRU) investigated the native plasticity of PD-1 at global (structural and dynamical) and local (residue side-chain orientations) levels by studying the interactive interfaces of PD-L1 and mAbs. The group observed that the structural stability and coordinated C_α movements are increased in the presence of PD-1's binding partners.

The rigorous analysis of these PPIs using computational biophysical approaches revealed PD-1's intrinsic plasticity, its concerted loops' movement (BC, FG, and CC'), distal side-chain motions, and the thermodynamic landscape, which are perturbed remarkably from its unbound to bound states. Based on intra-/inter-residues' contact networks and energetics, the hot-spots have been identified that were found to be essential to arrest the dynamical motions of PD-1 significantly for the rational design of therapeutic agents by mimicking the mAbs mechanism.

Complete paper at: https://pubmed.ncbi.nlm.nih.gov/33433201/

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