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Characterizing allosteric communication in h-cisPT enzyme through network and transfer entropy analysis

The human cis-prenyl-transferase is an enzyme involved in isoprenoid synthesis formed by a catalytic subunit and an auxiliary subunit. The purpose of our work was to understand the mechanism through which the S249V mutation, outside the catalytic subunit, can affect the activity of the enzyme.

We first built a protein network where the arc weights were related to the correlation of the two residues. We then computed the paths of minimal length connecting each residue with all other residues, and finally, the centrality index (CI) that represents the fraction of minimal paths a residue sits on.

The paths where the mutation caused the highest relative increase of length were those originating from the critical S249 residue. Moreover, the highest peak of the CI corresponded to the βD-βE loop where S249 lies, and this peak was turned into a minimum by the S249V mutation. The analysis thus suggested that the S249V mutation decreased the number of pathways transiting through the critical S249 residue impairing the coupling between different regions of the protein.

In order to identify the starting and final points of the key pathways affected by the mutation, we performed an analysis of Transfer Entropy that quantifies the coupling between two residues. The TE can be either computed from long MD simulations or from single structures using a Gaussian Network Model (GNM). In our work we employed a hybrid approach, averaging the GNM TE over all frames of a MD simulation.

The TE analysis revealed that the most important TE donors were the mobile peripheral helices. The largest cluster of TE acceptors instead, was located on the walls of the catalytic pocket. Choosing the TE donors as starting points and the TE acceptors as destinations, we attained pathways passing through the βD-βE loop that thus acted as a hub of the communication network. This suggested that the S249V mutation would interrupt most pathways connecting TE donors and acceptors.

Role

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