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Interactions of Focal Adhesion Kinase as a Drug Target for Pathological Cardiac Hypertrophy

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Abstract—*The focal adhesion targeting (FAT) domain of focal adhesion kinase is imnplicated in pathological cardiac hypertrophy leading to heart failure. Two crystal forms of the FAT domain are known, namely; arm exchanged (ae) dimer and closed (c) four helical monomeric bundle. The cFAT domain mediates interaction with Paxillin, and is responsible for proper functioning of the heart. An intermediate open (o) form of FAT interacts with Grb2 and leads to pathological cardiac hypertrophy. In this work, we carried out targeted Molecular Dynamics simulations using Amber in order to study the conformational transition of FAT and capture the pathologically relevant oFAT structure. The stages of the transformation were identified and cross-correlation between the molecular motions during the trajectory was plotted. Further, oFAT was docked with Grb2 and MD simulation of the complex was carried out. Conservation analysis of the binding site was carried out using Consurf. The open intermediate structure captured in the transition process during TMD shows an exposed Grb2 binding site due to opening of Helix1. Transition state analysis revealed that Helix1 unfolding and displacement had a significant impact on loop 3 residues and overall orientation of the helix bundle. The overall shift in orientation of all the four helices rejects Paxillin binding and approves Grb2 association during the transition. Binding site analysis helped to determine the residues responsible for binding and specificity. The modeled oFAT-Grb2 complex provides a structural basis for pharmacological modulation of FAT-Grb2 interaction by a small molecule antagonist. A second strategy to stop the disease progression was also proposed, namely to introduce high affinity paxillin-LD4 analogs that can stabilize cFAT to favor the healthy state. Our work will help develop structure-based strategies for prevention and treatment of pathological cardiac hypertrophy.*