



Category: Bioinformatics

Targeted Molecular Dynamics to determine Focal Adhesion Targeting Domain Folding Intermediates

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Abstract

The Focal adhesion kinase (FAT) domain of Focal Adhesion Kinase is a four helical bundle known for conformational plasticity. FAT adopts two distinctly different conformations i.e., close (cFAT) and arm-exchanged (aeFAT) states under native conditions [1]. The slow transition from cFAT to aeFAT is likely to proceed through an open intermediate state that allows YENV motif to attain β -turn conformation and phosphorylation of Y925 by Src kinases [2]. The two end states of FAT are known to interact with Paxillin and are responsible for maintaining steady state in Heart while intermediate conformation interacts with Grb2-SH2 leading to Pathological Cardiac Hypertrophy (PAH) [2]. 10ns Targeted Molecular Dynamics (TMD) was done between c- and aeFAT in order to explore the conformational transition and to capture pathologically relevant oFAT. Cluster and dynamic cross correlation analysis (DCCA) of TMD generated trajectory was done and the selected FAT intermediate was docked with Grb2-SH2 using HADDOCK v2.2 docking followed by molecular dynamics. Conservation analysis of FAT-Grb2 binding site was done using CONSURF [3]. A Pharmacophore FAT-Grb2 complex was generated using SPARKv1.2 and submitted for Virtual screening using BLAZE v4. Drug likeliness and ADMET properties were calculated using MOLINSPIRATION tool. TMD reveals six clusters and DCCA showed positively and negatively correlated region along the transition pathway. Intermediates with competence for Grb2 interaction were docked with Grb2 and best binding complex was further refined. MMPBSA binding energy calculations revealed the best binding pose where the phosphorylated YENV motif of Human FAT interacted with a charged and hydrophobic pocket of Grb2. The conservation analysis showed that the charged pocket was more conserved in comparison with the hydrophobic pocket, hence providing useful insights on binding and specificity determining residues in Grb2. Virtual screening using the pharmacophore yielded 3829 hits out of ~10 lakh ligand library. Further ADMET refinement and AUTODOCK batch docking identified five high affinity inhibitors for disruption of the oFAT-Grb2 interface. Pharmacological modulation of the FAT-Grb2 interaction will help in the development of selective inhibitors against PAH.

References

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