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Structural Molecular Dynamics Modelling of FH2 Domain of Formin DAAM

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Abstract : FH2 (formin homology-2) domains of several proteins, collectively known as formins, including DAAM, DAAM1 and mDia1, promote G-actin nucleation and elongation. FH2 domains of these formins exist as oligomers. Chain dimerization by ring structure formation serves as a structural basis for actin polymerization function of FH2 domain. Proper single chain configuration and specific interactions between its various regions are necessary for individual chains to form a dimer functional in G-actin nucleation and elongation. FH1 and WH2 domain-containing formins were shown to behave as intrinsically disordered proteins. Thus, the aim of this research was to study structural dynamics of FH2 domain of DAAM. To investigate structural features of FH2 domain of DAAM, molecular dynamics simulation of chain A of FH2 domain of DAAM solvated in water box in 50 mM NaCl was conducted at temperatures from 293.15 to 353.15K, with VMD 1.9.2, NAMD 2.14 and Amber Tools 21 using 2z6e and 1v9d PDB structures of DAAM was obtained on I-TASSER webserver. Calcium and ATP bound G-actin 3hbt PDB structure was used as a reference protein with well-described structural dynamics of denaturation. Topology and parameter information of CHARMM 2012 additive all-atom force fields for proteins, carbohydrate derivatives, water and ions were used in NAMD 2.14 and ff19SB force field for proteins in Amber Tools 21. The systems were energy minimized for the first 1000 steps, equilibrated and produced in NPT ensemble for 1ns using stochastic Langevin dynamics and the particle mesh Ewald method. Our root-mean square deviation (RMSD) analysis of molecular dynamics of chain A of FH2 domains of DAAM revealed similar insignificant changes of total molecular average RMSD values of FH2 domain of these formins at temperatures from 293.15 to 353.15K. In contrast, total molecular average RMSD values of G-actin showed considerable increase at 328K, which corresponds to the denaturation of G-actin molecule at this temperature and its transition from native, ordered, to denatured, disordered, state which is well-described in the literature. RMSD values of lasso and tail regions of chain A of FH2 domain of DAAM exhibited higher than total molecular average RMSD at temperatures from 293.15 to 353.15K. These regions are functional in intra- and interchain interactions and contain highly conserved tryptophan residues of lasso region, highly conserved GNYMN sequence of post region and amino acids of the shell of hydrophobic pocket of the salt bridge between Arg171 and Asp321, which are important for structural stability and ordered state of FH2 domain of DAAM and its functions in FH2 domain dimerization. In conclusion, higher than total molecular average RMSD values of lasso and post regions of chain A of FH2 domain of DAAM may explain disordered state of FH2 domain of DAAM at temperatures from 293.15 to 353.15K. Finally, absence of marked transition, in terms of significant changes in average molecular RMSD values between native and denatured states of FH2 domain of DAAM at temperatures from 293.15 to 353.15K, can make it possible to attribute these formins to the group of intrinsically disordered proteins rather than to the group of intrinsically ordered proteins such as G-actin.

Keywords : FH2 domain, DAAM, formins, molecular modelling, computational biophysics
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