All-atom simulations of structures and energetics of c-di-GMP-bound and free PleD

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Cyclic diguanosine monophosphate is a bacterial second messenger involved in a lifestyle switch from single cells to biofilm formation. Atomistic simulations are used to characterize inhibited diguanylate cyclase (DGC) PleD with emphasis on the feedback inhibition mechanism. Normal-mode calculations show a rigidification particularly in both the inhibition site and the active site of the protein upon ligand binding. Extensive molecular dynamics simulations in explicit solvent and analysis of the dynamical cross-correlation maps suggest two distinct coupling pathways between the active and the inhibition site: direct information transfer either through the beta-strands beta2 and beta3 of the DGC domain (pathway I) or via the disordered regions connecting domains D2 and DGC (pathway II). In addition, dynamical cross-correlation maps show differences in the correlation between neighboring domains upon ligand binding and upon the point mutation R390A. The correlated motions between domains D1 and D2, which form the dimerization interface, are stronger for free PleD. Complementary to the experimentally observed short-range interactions in ligated PleD, the present work also characterizes the long-range, delocalized interactions between domains that are important for understanding activation and allosteric control of the protein. Based on the results, experimental characterization of the point mutant R353 and of the double mutant N357/H394 is proposed to differentiate between pathways I and II.
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