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Title: Molecular mechanism of allosteric regulation of an intrinsically disordered protein, sortase, revealed by comprehensive all-atom conformational sampling simulations

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Dynamic changes in the conformational spaces of intrinsically disordered proteins (IDPs) in response to binding of target molecules are directly related to how the IDPs regulate their functions such as molecular recognition and cellular signaling. In case of an IDP, sortase, a loop (disordered loop) undergoes a disordered-to-ordered transition together with the tilt of another loop (dynamic loop) on binding of a signal peptide and a calcium ion. Here, as a novel challenge of computational biophysics, all-atom conformational ensembles of sortase for a complete set of binding states were calculated by our newly developed multiscale enhanced sampling (MSES) simulation to examine how the conformational ensembles change via the peptide and/or the calcium bindings. The MSES simulation was introduced to enhance the all-atom conformations with explicit solvent by coupling with the accelerated dynamics of the C?-atom coarse grained model. A 100-ns MSES simulation of the free sortase (without the peptide and calcium bound) using 20 replicas (i.e., the total simulation time is 2 ?s) clarified that the free sortase have really a flexible loop. The bound states MSES simulations showed dynamic changes of the free energy landscapes upon the peptide/calcium bindings, indicating that the weak hydrophobic interaction via peptide binding shifts the population from the unbound to bound structures (?population shift?) while the strong, long-range interaction via calcium ion enforces the bound structure (?induced fit?). The bound calcium facilitates the affinity of the signal peptide binding by inducing the folded structure of the disordered loop and stabilizing the formation of the peptide binding pocket, which is the molecular mechanism of the allosteric regulation by calcium ion.