OMICS Group Conferences
Accelerating Scientific Discovery

International Conference on
Central Nervous System - Drug Effects & Novel Drug Development

September 5-7, 2012 DoubleTree by Hilton Philadelphia Center City, USA

Impact of chemical heterogeneity on protein self-assembly in water

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Hydrophobicity is thought to underlie self-assembly in biological systems. However, the protein surface comprises hydrophobic and hydrophilic patches, and understanding the impact of such a chemical heterogeneity on protein self-assembly in water is of fundamental interest. Here, we report structural and thermodynamic investigations on the dimer formation of full-length amyloid-β proteins in water associated with Alzheimer's disease. Spontaneous dimerization process-from the individual diffusive regime at large separations, through the approach stage in which two proteins come close to each other, to the structural adjustment stage toward compact dimer formation-was captured in full atomic detail via unguided, explicit-water molecular dynamics simulations. The integral-equation theory of liquids was then applied to simulated protein structures to analyze hydration thermodynamic properties and the water-mediated interaction between proteins. We demonstrate that hydrophilic residues play a key role in initiating the dimerization process. A long-range hydration force of enthalpic origin acting on the hydrophilic residues provides the major thermodynamic force that drives two proteins to approach from a large separation to a contact distance. After two proteins make atomic contacts, the nature of the water-mediated interaction switches from a long-range enthalpic attraction to a short-range entropic one. The latter acts both on the hydrophobic and hydrophilic residues. Along with the direct protein-protein interactions that lead to the formation of intermonomer hydrogen bonds and van der Waals contacts, the water-mediated attraction of entropic origin brings about structural adjustment of constituent monomer proteins toward the formation of a compact dimer structure.

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