UNDERSTANDING THE STRUCTURE AND APO-DYNAMICS OF JIP1

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Alzheimer's Disease (AD) is a multifaceted, complex disease with many potential causes. The Parish research group is working on the hypothesis that the Kinesin Light Chain protein (KLC1) is responsible for transporting amyloid precursor protein (APP), and misregulation of this process is a causative factor in AD. Recent experiments indicate that C-Jun Amino-Terminal Kinase-Interacting Protein 1 (JIP1) is likely important in the binding of KLC1 and APP. It has also been shown that JIP1 may increase the phosphorylation of tau by facilitating the interaction between the tau protein and c-Jun N-terminal kinase protein (JNK), which could also be a causative factor in AD. Very little is known about JIP1, and because it could be a vital component of the AD mechanism, molecular dynamics (MD) simulations using AMBER 14 were used to study the structure and apo-dynamics of this protein. It has been indicated experimentally that a short fragment of 11 residues within the JIP1 protein retain the full function of the molecule. A crystal structure of 10 of the 11 residues was available (PDBID=2H96) and used to study the structure and apo-dynamics of this short fragment. 2μs of conventional MD was performed on the JIP1 fragment in 10 different seeds, and from this, 7 energetically and structurally stable conformations of the 10-mer protein were found. These were compared to 10 different homology structures to determine whether there was structural agreement between the fragment and the entire 711 residue molecule. Markov State Modeling was used to create representations of the various seeds containing stable conformations. Knowing these conformations could help to understand the general dynamics of the protein and its interactions with other proteins like APP and KLC1.