COMPUTATIONAL INSIGHTS INTO SUBSTRATE RECOGNITION AND REACTIVITY OF ß-SECRETASE (BACE1) ENZYME

Arghya Barman and Rajeev Prabhakar
Department of chemistry, University of Miami, 1301 memorial drive, Coral gables, FL 33146

Beta secretase (BACE1) is an aspartyl protease that catalyzes the rate limiting step of the formation Alzheimer amyloid-β peptides (Aβ). In comparison to WT substrate, BACE1 hydrolyzes a double mutant of amyloid precursor protein (APP) (Lys670→Asn and Met671→Leu) known as Swedish mutant (SW) with sixty times higher kcat/Km value. We have applied classical molecular dynamics (MD) simulation to elucidate the interactions of both the substrates with BACE1 and further employed DFT approach to investigate their cleavage mechanisms. Our results show that the SW substrate adopts more productive conformation inside BACE1 and hydrolyzed by 3.3 Kcal/mol lower barrier than the one computed for the WT substrate. The GPI anchored BACE1 shows differential activity on +1 (Met_{-1}-Asp_1) and +11 (Tyr_{10}-Glu_{11}) cleavage site of APP. We have investigated investigate the structural differences of BACE1 induced by GPI through MD simulations