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Exploring Beta-Amyloid Protein Transmembrane Insertion Behavior and Residue-Specific Lipid Interactions in Lipid Bilayers Using Multiscale MD Simulations[1] LIMING QIU, MARK VAUGHN, KELVIN CHENG, Texas Tech University — Beta-amyloid (Abeta) interactions with neurons are linked to Alzheimer's. Using a multiscale MD simulation strategy that combines the high efficiency of phase space sampling of coarse-grained MD (CGD) and the high spatial resolution of Atomistic MD (AMD) simulations, we studied the Abeta insertion dynamics in cholesterol-enriched and -depleted lipid bilayers that mimic the neuronal membranes domains. Forward (AMD-CGD) and reverse (CGD-AMD) mappings were used. At the atomistic level, cholesterol promoted insertion of Abeta with high (folded) or low (unfolded) helical contents of the lipid insertion domain (Lys28-Ala42), and the insertions were stabilized by the Lys28 snorkeling and Ala42-anchoring to the polar lipid groups of the bilayer up to 200ns. After the forward mapping, the folded inserted state switched to a new extended inserted state with the Lys28 descended to the middle of the bilayer while the unfolded inserted state migrated to the membrane surface up to 4000ns. The two new states remained stable for 200ns at the atomistic scale after the reverse mapping. Our results suggested that different Abeta membrane-orientation states separated by free energy barriers can be explored by the multiscale MD more effectively than by Atomistic MD simulations alone.

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