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Role of sequence and membrane composition in structure of transmembrane domain of Amyloid Precursor Protein

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Aggregation of proteins of known sequence is linked to a variety of neurodegenerative disorders. The amyloid β (Aβ) protein associated with Alzheimer's Disease (AD) is derived from cleavage of the 99 amino acid C-terminal fragment of Amyloid Precursor Protein (APP-C99) by γ-secretase. Certain familial mutations of APP-C99 have been shown to lead to altered production of Aβ protein and the early onset of AD. We describe simulation studies exploring the structure of APP-C99 in micelle and membrane environments. Our studies explore how changes in sequence and membrane composition influence (1) the structure of monomeric APP-C99 and (2) APP-C99 homodimer structure and stability. Comparison of simulation results with recent NMR studies of APP-C99 monomers and dimers in micelle and bicelle environments provide insight into how critical aspects of APP-C99 structure and dimerization correlate with secretase processing, an essential component of the Aβ protein aggregation pathway and AD.