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Structure of APP-C99$_{1-99}$ and Implications for Role of Extra-Membrane Domains in Function and Oligomerization

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Abstract

The 99 amino acid C-terminal fragment of Amyloid Precursor Protein APP-C99 (C99) is cleaved by γ-secretase to form Aβ peptide, which plays a critical role in the etiology of Alzheimer's Disease (AD). The structure of C99 consists of a single transmembrane domain flanked by intra and intercellular domains. While the structure of the transmembrane domain has been well characterized, little is known about the structure of the flanking domains and their role in C99 processing by γ-secretase. To gain insight into the structure of full-length C99, REMD simulations were performed for monomeric C99 in model membranes of varying thickness. We find equilibrium ensembles of C99 from simulation agree with experimentally-inferred residue insertion depths and protein backbone chemical shifts. In thin membranes, the transmembrane domain structure is correlated with extra-membrane structural states and the extra-membrane domain structural states become increasingly decorrelated to each other. Mean and variance of the transmembrane and $G_{37}G_{38}$ hinge angles are found to increase with thinning membrane. The N-terminus of C99 forms β-strands that may seed aggregation of Aβ on the membrane surface, promoting amyloid formation. The N-terminus, which forms α-helices that interact with the nicastrin domain of γ-secretase. The C-terminus of C99 becomes more α-helical as the membrane thickens, forming structures that may be suitable for binding by cytoplasmic proteins, while C-terminal residues essential to cytotoxic function become α-helical as the membrane thins. The heterogeneous but discrete extra-membrane domain states analyzed here open the path to new investigations of the role of C99 structure and membrane in amyloidogenesis.

Introduction