Characterizing γ-secretase, responsible for the generation of amyloid-β peptides

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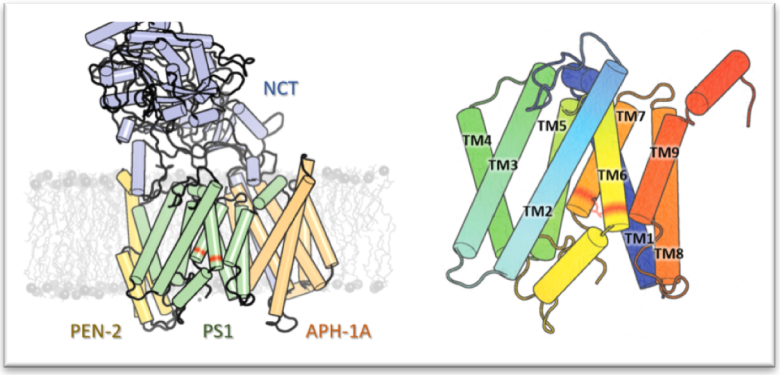

γ-secretase is an intramembrane-cleaving aspartyl protease that plays an essential role in the processing of a variety of integral membrane proteins. Its role in the ultimate cleavage step in the processing of amyloid precursor protein to form amyloid-β (Aβ) peptide makes it an important therapeutic target in Alzheimer's disease research. Significant recent advances have been made in structural studies of this critical membrane protein complex. However, details of the mechanism of activation of the enzyme complex remain unclear. Using a multiscale computational modeling approach, combining multiple coarse-grained microsecond dynamic trajectories with all-atom models, we evaluated (1) the overall γ-secretase structural ensemble, (2) identified its two conformational states associated to an active and inactive enzyme, and (3) studied the influence of membrane lipid composition on the structure and activity of γ-secretase.