A029 · Decoding the Thermodynamic Competition Between APP-C99 Dimerization and Membrane Partitioning

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Session: Day 1 · Thu Oct 1, 2026 · 2:15–4:15 PM

Membrane proteins experience multiple coupled thermodynamic driving forces that determine both where they localize and how they assemble, yet these contributions are often analyzed separately. Here, we quantify the competition between membrane partitioning and dimerization for the amyloid precursor protein C-terminal fragment C99 (APP-C99), the direct precursor of amyloid-β. Using coarse-grained molecular dynamics and enhanced-sampling free-energy calculations, we determined C99 dimerization free energies in liquid-ordered (Lo) and liquid-disordered (Ld) membranes and the free-energy cost of partitioning between these environments across multiple cholesterol compositions. Dimerization is markedly more favorable in ordered membranes, with association free energies approximately 7–9 kcal/mol more favorable than in disordered membranes. However, this energetic gain is counteracted by a substantial penalty for transferring C99 from the disordered to the ordered phase. Combining these quantities within a thermodynamic cycle reveals that the membrane environment that most strongly stabilizes the dimer is not necessarily the environment in which the dimer is thermodynamically preferred. Thus, protein association and membrane localization must be considered as coupled processes rather than independent determinants of membrane organization. More broadly, this framework provides a systematic route for decomposing and recombining the free-energy contributions governing membrane-protein assembly. Because the individual thermodynamic terms can be evaluated in arbitrary membrane environments, the same strategy can be extended from model Lo/Ld systems to realistic multicomponent membranes representing distinct cellular organelles and membrane contact sites, enabling direct assessment of how membrane composition reshapes protein localization and oligomerization.

Decoding the Thermodynamic Competition Between APP-C99 Dimerization and Membrane Partitioning

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Abstract

Membrane proteins experience multiple coupled thermodynamic driving forces that determine both where they localize and how they assemble, yet these contributions are often analyzed separately. Here, we quantify the competition between membrane partitioning and dimerization for the amyloid precursor protein C-terminal fragment C99 (APP-C99), the direct precursor of amyloid-β. Using coarse-grained molecular dynamics and enhanced-sampling approaches, we determined C99 dimerization free energies in liquid-ordered (L_o) and liquid-disordered (L_d) membranes and the free-energy cost of partitioning between these environments across multiple cholesterol compositions. Dimerization is markedly more favorable in ordered membranes, with association free energies approximately 7-9 kcal mol^{-1} more favorable than in disordered membranes. However, this energetic gain is counteracted by a substantial penalty for transferring C99 from the disordered to the ordered phase. Combining these quantities within a thermodynamic cycle reveals that the membrane environment that most strongly stabilizes the dimer is not necessarily the environment in which the dimer is thermodynamically preferred. Thus, protein association and membrane localization must be considered as coupled processes rather than independent determinants of membrane organization. More broadly, this framework provides a systematic route for decomposing and recombining the free-energy contributions governing membrane-protein assembly. Because the individual thermodynamic terms can be evaluated in arbitrary membrane environments, the same strategy can be extended from model L_o/L_d systems to realistic multicomponent membranes representing distinct cellular organelles and membrane contact sites, enabling direct assessment of how membrane composition reshapes protein localization and oligomerization.