**Presenilin, γ-secretase and the search for pathogenic triggers in Alzheimer's disease**

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Mutations that cause early-onset familial Alzheimer's disease (FAD) are in the substrate and enzyme that produce the amyloid β-peptide (Aβ), with the 42-residue form (Aβ42) pathologically depositing as cerebral plaques. FAD mutations in the amyloid precursor protein (APP) and presenilin, the catalytic component of the γ-secretase complex, alter processive proteolysis of APP substrate to skew the proportion of longer, aggregation-prone Aβ peptides and increase the Aβ42/Aβ40 ratio, long considered important for triggering pathogenesis. However, not all FAD mutations increase this ratio, and the large majority decrease overall proteolytic activity, resulting in reduced Aβ production. We recently reported evidence that FAD mutations commonly lead to reduction in early cleavage steps in the processive proteolysis of APP substrate by γ-secretase due to stalling of enzyme-substrate (E-S) complexes (Devkota *et al., Cell Reports*, 2024; Arafi *et al., eLife*, 2025). Development of a *C. elegans* model system for FAD led to the finding that stalled and stabilized γ-secretase E-S complexes are sufficient to induce age-dependent synaptic loss and reduced lifespan, independent of Aβ production. Thus, the stalled process—not the products—of γ-secretase proteolytic processing can cause synaptic degeneration. These findings raise the question of whether stalled E-S complexes—not Aβ42—is the primary disease driver in FAD. New unpublished results in support of the "stalled complex hypothesis" and its relevance to the pathogenesis of late-onset sporadic AD will be presented.

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