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Restricted Location of PSEN2/γ-Secretase Determines Substrate Specificity and Generates an Intracellular Aβ Pool.

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Abstract

γ-Secretases are a family of intramembrane-cleaving proteases involved in various signaling pathways and diseases, including Alzheimer's disease (AD). Cells co-express differing γ-secretase complexes, including two homologous presenilins (PSENs). We examined the significance of this heterogeneity and identified a unique motif in PSEN2 that directs this γ-secretase to late endosomes/lysosomes via a phosphorylation-dependent interaction with the AP-1 adaptor complex. Accordingly, PSEN2 selectively cleaves late endosomal/lysosomal localized substrates and generates the prominent pool of intracellular Aβ that contains longer Aβ; familial AD (FAD)-associated mutations in PSEN2 increased the levels of longer Aβ further. Moreover, a subset of FAD mutants in PSEN1, normally more broadly distributed in the cell, phenocopies PSEN2 and shifts its localization to late endosomes/lysosomes. Thus, localization of γ-secretases determines substrate specificity, while FAD-causing mutations strongly enhance accumulation of aggregation-prone Aβ42 in intracellular

acidic compartments. The findings reveal potentially important roles for specific intracellular, localized reactions contributing to AD pathogenesis.

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