

ORAL PRESENTATION

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Regulation of dynamic BACE1 trafficking in neurons

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Proteolytic processing of amyloid precursor protein (APP) by β -site APP cleaving enzyme 1 (BACE1) and γ -secretase generates A β peptides. APP is constitutively trafficked through the secretory and endocytic pathways in cultured cells and neurons. The identities of cellular organelles and sorting pathways involved in amyloidogenic processing of APP have been extensively investigated. Although a consensus has not yet emerged, there is a general agreement from biochemical and genetic studies on the importance of endocytic APP trafficking for A β production. In neurons, APP is trafficked anterogradely along peripheral and central axons, and proteolytically processed during transit. Recent *in vivo* studies estimated that ~70% of A β released in the brain requires ongoing endocytosis, and synaptic activity regulates the vast majority of this endocytosis-dependent A β . BACE1 cleavage is thought to be the rate-limiting step in amyloidogenic processing of APP. Little, however, is known about endocytic BACE1 sorting and dynamic transport in neurons. We investigated BACE1 trafficking in cultured hippocampal neurons using live-cell imaging and selective labeling. This approach revealed dynamic neuronal transport of internalized BACE1 in dendrites and axons. BACE1 was transported in vesicles that were positive for markers of recycling endosomes. Dominant-negative expression and siRNA knock-down of proteins involved in endocytic transit revealed that BACE1 is dynamically transported in recycling endosomes and this process significantly contributes to amyloidogenic APP processing. Our results suggest that BACE1 trafficking in neuronal recycling endosomes is likely relevant for presynaptic A β production and contributes to Alzheimer's disease pathogenesis.

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