# Endocytosis of synaptic ADAM10 in neuronal plasticity and Alzheimer's disease

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**A disintegrin and metalloproteinase 10 (ADAM10), a disintegrin and metalloproteinase that resides in the postsynaptic densities (PSDs) of excitatory synapses, has previously been shown to limit β-amyloid peptide (Aβ) formation in Alzheimer's disease (AD). ADAM10 also plays a critical role in regulating functional membrane proteins at the synapse. Using human hippocampal homogenates, we found that ADAM10 removal from the plasma membrane was mediated by clathrin-dependent endocytosis. Additionally, we identified the clathrin adaptor AP2 as an interacting partner of a previously uncharacterized atypical binding motif in the ADAM10 C-terminal domain. This domain was required for ADAM10 endocytosis and modulation of its plasma membrane levels. We found that the ADAM10/AP2 association was increased in the hippocampi of AD patients compared with healthy controls. Long-term potentiation (LTP) in hippocampal neuronal cultures induced ADAM10 endocytosis through AP2 association and decreased surface ADAM10 levels and activity. Conversely, long-term depression (LTD) promoted ADAM10 synaptic membrane insertion and stimulated its activity. ADAM10 interaction with the synapse-associated protein-97 (SAP97) was necessary for LTD-induced ADAM10 trafficking and required for LTD maintenance and LTD-induced changes in spine morphogenesis. These data identify and characterize a mechanism controlling ADAM10 localization and activity at excitatory synapses that is relevant to AD pathogenesis.**