ADAM10 at the Synapses: New Perspectives on Alzheimer disease Pathogenesis

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Generation of Amyloid beta peptide is at the beginning of a cascade that leads to Alzheimer's disease (AD). Amyloid precursor protein, as well as beta- and gamma-secretases, are the principal players involved in Amyloid beta production, while alpha-secretase cleavage on APP prevents Abeta deposition. A disintegrin and metalloproteinase 10 (ADAM10) has been recently demonstrated to be alpha-secretase in neurons. Moreover, ADAM10 is a sheddase for many neuronal proteins and is located at the glutamatergic postsynaptic density. Although localization of ADAM10 in the synaptic membrane is key for its shedding activity, currently very little is known about the mechanisms that control the synaptic abundance of ADAM10.

Here we report a novel mechanism to finely tune synaptic availability and activity of ADAM10. We show that ADAM10 removal from the plasma membrane is mediated by clathrin-dependent endocytosis and describe the clathrin adaptor AP2, a heterotetrameric assembly which initiates the endocytosis process, as new interacting partner of ADAM10 C-terminal domain. In particular, we identify a previously uncharacterized atypical binding motif for AP2 complex in ADAM10 cytoplasmic tail, which is relevant for ADAM10 endocytosis and for the modulation of its plasma membrane levels.

Moreover, we describe a pathological alteration of ADAM10/AP2 association in AD and a physiological role in activity-dependent synaptic plasticity. Long-term potentiation induces ADAM10 endocytosis, through AP2 association, and decreases surface ADAM10 levels and activity. Conversely, long-term depression (LTD) promotes ADAM10 synaptic membrane insertion and stimulates its activity. Furthermore, ADAM10 interaction with the synapse-associated protein-97 (SAP97) is necessary for LTD-induced ADAM10 trafficking and required for LTD maintenance and LTD-induced changes in spine morphogenesis. Together, our data disclose a novel physiological mechanism controlling ADAM10 localization and activity at excitatory synapses, which involves regulated interactions with SAP97 and AP2 and which is relevant for AD pathogenesis. Moreover, the characterization of SAP97 and AP2 interaction and function in activity-dependent synaptic plasticity gives new insights on possible therapeutic targets of AD.