ADAM10 exocytosis/endocytosis in spines: looking for new therapeutic strategies

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Alzheimer's disease (AD) is the most common neurodegenerative disorder characterized by progressive loss of synapses and neurons and accumulation of insoluble deposits of amyloid beta-peptide (Aβ). Although AD is emerging as the most prevalent and socially disruptive illness of aging populations, it is currently incurable. Aβ derives from the amyloid precursor protein (APP), which can follow 2 mutually exclusive pathways in the cell. The amyloidogenic pathway involves BACE and gamma secretase activities and leads to Aβ formation (Vassar et al., 1999). On the other hand, the main protagonist of the non-amyloidogenic pathway is ADAM10, a disintegrin and metalloproteinase 10, which cleaves APP in the domain corresponding to Aβ, thus precluding Aβ production (Lammich et al., 1999). Since the modulation of ADAM10 synaptic localization through ADAM10 membrane insertion/removal could constitute an innovative therapeutic strategy to finely tune its shedding activity, we have investigated the mechanisms underlying ADAM10 endocytosis.
We show that ADAM10 removal from the plasma membrane is mediated by clathrin-dependent endocytosis and we 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 an atypical binding motif for AP2 complex in ADAM10 cytoplasmic tail, which is relevant for ADAM10 endocytosis and the modulation of its plasma membrane levels. Moreover, we describe a pathological alteration of ADAM10/AP2 association in AD patients. On the basis of these findings, we designed four cell permeable peptides (CPPs) able to interfere with ADAM10/AP2 association and, thereby, to reduce ADAM10 endocytosis. We demonstrate, both with *in vitro* and *in vivo* experiments, that two of four CPPs are able to disrupt ADAM10/AP2 interaction and to increase the levels of ADAM10 at synapsis membrane.
Several studies highlighted the key role of ADAM10 in health and disease, due to its shedding activity toward a number of functional membrane proteins such as APP and N-cadherin (Malinverno et al., 2010). Through its shedding activity, ADAM10 has been shown to regulate key cellular functions including cell growth, adhesion, and migration and spine stabilization in excitatory neuron (Seals et al., 2003). A finely balanced membrane level of ADAM10 is an essential prerequisite to control enzyme activity and its functions. We designed a powerful tool able to interfere with mechanisms regulating intracellular trafficking of ADAM10 and to modulate its membrane availability, and thereby to shift APP metabolism toward non amyloidogenic pathway. In the light of above, the use of CPPs is a key starting point to develop new therapeutic strategy for Alzheimer's disease.

References

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