CAP2, a regulator of actin filament dynamic, is a novel ADAM10 interactor.

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Alzheimer's disease (AD) is a progressive and neurodegenerative disorder, characterized by increased levels of amyloid β-peptides (Aβ) and their deposition as senile plaques. In particular, it has been shown that Aβ plays a prominent role in AD pathology by inducing synapse loss and subsequent cognitive deficits. Aβ derives from the Amyloid Precursor Protein (APP), which can be sequentially cleaved by the protease BACE1 and by the γ-secretase to produce Aβ. Otherwise, APP can be cleaved by Î±-secretase (ADAM10), that cleaves APP within the Aβ domain, thus preventing Aβ generation. Furthermore in neurons, ADAM10 works as sheddase of several adhesion molecules, such as neuroligin-1, N-cadherin, NCAM and Ephrin. Therefore, in a wider framework, ADAM10 makes a large contribution in controlling spine morphology and activity-dependent plasticity. Given the key role played by ADAM10 in the amyloid cascade and in controlling synaptic morphology, ADAM10 can represent a potential target to affect the synaptic failure in AD. ADAM10 cleaves its substrates only when it is inserted at the plasma membrane. Therefore, the intracellular trafficking of ADAM10 represents a mechanism capable of tuning its activity and is regulated by the interaction with different partners. In light of these considerations, to identify novel protein partners of ADAM10, we performed a yeast two-hybrid screening, using ADAM10 C-terminal tail as a bait. The results revealed CAP2 as a new ADAM10 binding partner. CAP2 is regulator of actin dynamics and could be involved in the modulation of ADAM10 subcellular distribution and activity in neurons. Here we confirmed ADAM10-CAP2 interaction by biochemical approaches and we identified the domain responsible for the association. Moreover, we defined the CAP2 sequence involved in actin binding and we analysed the effect of this interaction on ADAM10 synaptic localization.
The characterization of ADAM10-CAP2 complex could favour the development of new experimental approaches to promote ADAM10 neuronal activity thus limiting Aβ generation.