Protein-protein interactions in Alzheimer's disease

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Research question and background

Molecular pathogenesis of Alzheimer Disease (AD) is the result of a complex interplay of crossing pathways. Accumulating evidences indicate the amyloid cascade as the primary event in the pathogenesis. Furthermore, AD exhibits abnormal synaptic functions. New theories are emerging associating synaptic and neuronal loss to Aβ oligomers. The complete understanding of the mechanism/s through which these two components of AD pathogenesis reciprocally interact and influence each other is becoming more and more important to reach a complete picture of the disease's molecular pathogenesis.

Based on these considerations, we aim at identifying new proteins involved in the cross-talk existing between the amyloid cascade and synaptic activity. We performed two hybrid screenings with either α-secretase ADAM10 cytoplasmic tail or the C-terminal domain (lacking the PDZ-binding domain) of the GluN2A subunit of the NMDA receptor. We identified the cyclase-associated protein 2 (CAP2) as ADAM10 binding partner and Ring Finger Protein 10 (RNF10) and Zinc transporter-1 (ZNT-1) as GluN2A interacting proteins. CAP2 is regulator of actin filament dynamics and could be involved in the modulation of ADAM10 subcellular distribution in neurons. RNF10 is a new synaptonuclear protein messenger, which responds to specific calcium signals at the postsynaptic compartment to elicit discrete changes at the transcriptional level. ZNT-1 is a transmembrane protein which pumps cytosolic Zn2+ to the extracellular space.

In light of these data, we consider all these protein potentially relevant for AD pathogenesis. Therefore, it is mandatory to explore these protein complexes in human hippocampi of AD patients and healthy control subjects, to evaluate a possible alteration of these interactions.

Methods and tissues used

We analysed autoptic hippocampus specimen from 6 AD patients (Braak 4 and Braak 5) and 6 healthy controls (HC). Total levels of RNF10, CAP2 and ZNT-1 have been assessed by biochemical analyses. Moreover, we measured the nuclear levels of RNF10.

Results and conclusion

Preliminary results show a significant reduction in RNF10 total and nuclear protein levels in AD patients' hippocampi compared to HC. As far as concern ZNT-1, we measured a significant increase of the total protein levels in AD patients compared to HC. On the other hand, the analysis of CAP2 total protein levels revealed a slight reduction in AD patients compared to HC. Based on these preliminary findings, we will analyze the synaptic localization of such proteins and the interaction with ADAM10 and GluN2A. The results will add new pieces to the puzzle in the understanding of the complex and coordinated events leading to AD pathogenesis.