STAD
Synapse-to-nucleus communication in Alzheimer's disease

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The main hypothesis of STAD predicted that an aberrant flux of information from the synapse to the nucleus could represent a fundamental element in the processes of alteration of synaptic function in Alzheimer's disease. The consortium successfully identified two different synapse-to-nucleus messengers, Jacob and RNF10, associated to different types of NMDA receptors and differentially modulated by activity-dependent synaptic plasticity.

Interesting results have been achieved analysing the putative impact of amyloid on Jacob. In particular, we showed that the CREB shut-off elicited by amyloid beta oligomers depends on the sustained activation of extrasynaptic GluN2B-containing NMDA receptor and the subsequent nuclear import of Jacob.
Furthermore, we characterized RNF10 as GluN2A-containing NMDA receptor-associated downstream signalling event. In analogy with what reported for Jacob, RNF10 is implicated in amyloid beta oligomers detrimental effects on neurons, possibly involving mitochondrial activity.

The consortium developed RNF10 knock out animals, and fully characterized a new phenotype. Interestingly, the animals show a lean phenotype, although not directly linked to peripheral insulin level. Activity-dependent synaptic plasticity events have been fully characterized in RNF10-/- animals, demonstrating a clear alteration of synaptic plasticity confined to a specific area of the hippocampus. The behavioural characterization fully paralleled molecular and electrophysiological studies, confirming RNF10-/- as new model of altered cognitive flexibility.

Overall, STAD helped in understanding the role of specific synaptonuclear messengers in amyloid dependent synaptic alterations through the development of innovative in vivo models.