THE CYCLASE-ASSOCIATED PROTEIN 2 IS A NOVEL REGULATOR OF COFILIN IN SYNAPTIC PLASTICITY AND ALZHEIMER'S DISEASE

Elena Marcello[1], Silvia Pelucchi[1,2], Lina Vandermeulen[1], Lara Pizzamiglio[3], Bahar Aksan[4], Jing Yan[4], Anja Konietzny[5], Elisa Bonomi[6], Barbara Borroni[6], Marco Rust[7,8,9], Daniele Di Marino[10], Marina Mikhaylova[5], Daniela Mauceri[4], Flavia Antonucci[3], Fabrizio Gardoni[1], Monica Di Luca[1]

[1] Department of Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, Milan, Italy; [2] Department of Neurosciences, Psychology, Drug Research, and Child Health, University of Florence, Florence - Italy; [3] Department of Biotechnology and Translational Medicine, Università degli Studi di Milano, Milan - Italy; [4] Department of Neurobiology, Interdisciplinary Centre for Neurosciences (IZN), Heidelberg University, Heidelberg - Germany; [5] Center for Molecular Neurobiology Hamburg (ZMNH), Emmy-Noether Group "Neuronal Protein Transport", University Medical Center Hamburg-Eppendorf (UKE), Hamburg - Germany; [6] Neurology Unit, Centre for Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Brescia - Italy; [7] Molecular Neurobiology Group; Institute of Physiological Chemistry; University of Marburg; Marburg - Germany; [8] DFG Research Training Group, Membrane Plasticity in Tissue Development and Remodeling, GRK 2213, Philipps-University of Marburg, Marburg - Germany; [9] Center for Mind, Brain and Behavior (CMBB), University of Marburg and Justus-Liebig-University Giessen, Marburg - Germany; [10] Polytechnic University of Marche, Department of Life and Environmental Sciences, Ancona - Italy

Introduction: Although Alzheimer's Disease (AD) is a definitive neurodegenerative disorder characterized by β-amyloid (Aβ) plaques and neurofibrillary tangles, much evidence supports synaptic dysfunction as a preceding and contributing insult to eventual neuronal death Dendritic spine loss is seen in post mortem brains from AD patients and in mice models of AD. In AD patients cognitive decline has a stronger correlation to synapse loss than to neurofibrillary tangles or neuronal loss. Diverse lines of evidence suggest that Aβ oligomers play a prominent role in AD synaptic dysfunction since they lead to dendritic spines loss and aberrant plasticity phenomena. To date, despite the relevance of synaptic dysfunction in the pathogenesis of AD, our knowledge of the mechanisms contributing to the frailty of synapses in AD is incomplete. The fact that AD is a disease of ageing, could suggest impairment in spine maintenance and can be related to an alteration of the pathways regulating the stability and remodeling of the actin cytoskeleton In the postsynaptic frame, cofilin is one of the master regulators of actin cytoskeleton dynamics. Even though cofilin activity can be modulated by phosphorylation of a single cofilin residue (ser3), non-phosphoregulatory mechanisms for cofilin activity also exist. In particular, long-term potentiation (LTP) induction triggers the translocation of cofilin into spines.

Methods: We used an array of different techniques, including biochemical and imaging assays, to assess the role of structural plasticity in AD and we validated our data in human tissue.

Results: Here, we describe the cyclase-associated protein 2 (CAP2) as a novel master regulator of cofilin localization in dendritic spines. CAP2 is a protein critical for neuronal architecture, spine morphology and synaptic function. The formation of CAP2 dimers through its Cys^{32} is important for CAP2 binding to cofilin and for normal spine actin turnover. We show that long-term potentiation (LTP) induction promotes the formation of Cys^{32}-dependent CAP2 dimers and association to cofilin. The CAP2 dimerization through Cys^{32} is necessary for LTP-induced cofilin translocation into spines, for spine remodeling and for the potentiation of synaptic transmission. Remarkably, in AD patients' hippocampi CAP2 is down-regulated, CAP2 dimer levels are reduced and cofilin is aberrantly localized in spines. In addition, this mechanism is an initial target of Aβ oligomers, which disrupt CAP2 association to cofilin and decrease the synaptic localization of both proteins..

Discussion and conclusions: Taken together, our comprehensive study identifies CAP2 as one of the so far unknown factors contributing to the loss of synaptic plasticity in AD. Therefore, our outcomes provide new insights into the molecular underpinnings leading to synaptic dysfunction, hence contributing to the development of tailored synapse-targeted therapies for AD.