THE ROLE OF ASTROCYTES IN COMPLEX COGNITIVE PROCESSING

João Filipe Viana[1,2], Sónia Guerra-Gomes[1,2], Daniela Sofia Abreu[1,2], João Luís Machado[1,2], Sara Barsanti[1,2], Mariana Gonçalves[1,2], Cristina Martín-Monteagudo[3], Vanessa Morais Sardinha[1,2], Diana Sofia Marques Nascimento[1,2], Gabriela Tavares[1,2], Martin Irmler[4], Johannes Beckers[4,5,6], Michal Korostynski[7], Nuno Sousa[1,2], Marta Navarrete[3], Andreia Teixeira-Castro[1,2], Luísa Pinto[1,2] & João Filipe Oliveira[1,2,8]

[1]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Portugal; [2]ICVS/3B's - PT Government Associate Laboratory, Portugal; [3] Instituto Cajal, CSIC, Madrid, Spain; [4]Institute of Experimental Genetics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany; [5]German Center for Diabetes Research (DZD), Germany; [6]Chair of Experimental Genetics, Technical University of Munich, Germany; [7]Laboratory of Pharmacogenomics, Department of Molecular Neuropharmacology, Maj Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland; [8]IPCA-EST-2Ai, Polytechnic Institute of Cávado and Ave, Applied Artificial Intelligence Laboratory, Portugal

Grant 37/18

Background: We and others showed previously that astrocytic modulation of neuronal activity affects the network activity and consequent output production. Astrocytes are active players in brain circuits, sensing and responding to neuronal activity, impacting behavior production. Activation of astrocytes triggers intracellular calcium elevations displaying complex spatiotemporal properties. Intracellular calcium activity is thought to underlie synaptic transmission, metabolism, and brain homeostasis modulation. However, the calcium-dependent signaling pathways involved in these processes are poorly understood, representing a critical knowledge gap in this field.

Aims: The main research objective of this project is to dissect the cellular mechanisms by which astrocytes influence cognitive function processed by cortico-limbic circuits.

Method: We tested mouse models that lack astrocytic signaling signaling to assess its role in cortico-limbic circuits. To assess the influence of these mechanisms to cognitive function, we used complementary state-of-the-art techniques such as *in vivo* electrophysiology, innovative behavior, structural and molecular analysis, to characterize and monitor cognitive function.

Results: The transcriptomic analysis of hippocampal tissue revealed that the lack of astrocytic somatic calcium causes the differential expression of hundreds of genes. Among these, 76 genes are regulated by the astrocyte-specific Foxo1 transcription factor. This transcription factor is over-expressed in the hippocampal astrocytes of this mouse model and regulates the expression of genes involved in spinogenesis and synaptic coverage. A detailed morphological analysis of hippocampal pyramidal neurons revealed dendrites with a shift to a more immature spine profile. This spine profile shift may underlie a previously described reduction of long-term depression and performance in fear memory tasks observed in this mouse model. Indeed, we confirmed that these mice lacking astrocytic somatic calcium display an enhancement of long-term memory. To verify a causal relationship between these structural, synaptic, and behavioral observations, we used a viral approach to induce the over-expression of Foxo1 in

hippocampal astrocytes in naïve C57BL/6J mice. This viral-driven over-expression of Foxo1 in astrocytes of the *stratum radiatum* replicated the shift to an immature spine profile in dendrites of pyramidal neurons crossing the territory of these astrocytes and led to a reduction of long-term depression in the same region. Finally, this manipulation was sufficient to enhance long-term memory.

Conclusions: The detailed characterization of the mouse model lacking astrocytic somatic calcium revealed that astrocytes modulate hippocampal circuit structure and function through Foxo1 signaling to enhance long-term memory.

Keywords: Cortico-limbic, Memory mechanism, Astrocyte

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E-mail contact: joaooliveira@med.uminho.pt