To visualize mitochondrial morphology, we will subretinally inject AAV2/6-CD68-mito-Dendra2 in *rd10* mice, or use a mitochondria-labeled mouse model for ONC. Changes in mitochondrial volume based on image rendering will identify connected or fragmented mitochondrial networks.
In both degenerative models, we observed reactive microglia based on increased Sholl intersections closer to the cell soma and an increased percentage of CD68 volume within microglia when compared to control. Importantly, this activation was found only in the synaptic layer with closest proximity to the degenerating neurons, while the furthest microglia were less reactive. Interestingly, we observed that microglia's average mitochondrial volume was significantly reduced not only in the expected synaptic layer proximal to neuronal degeneration for each model, but in both synaptic layers. The reduction in the average mitochondrial volume per microglia indicates a more fragmented mitochondrial network. Since the microglia furthest from degenerating neurons remain less active, but show mitochondrial fragmentation, we predict that this could be an intermediate phase of the microglia transition. Together, these data suggest that mitochondria morphology may be an early indicator for the microglia reactive state and a potential target for microglia modulation.

T05-033A

Dissecting the microglial response in transgenic models of amyloidogenesis and tauopathy

R. Sanchez-Varo[1], J.J. Fernandez-Valenzuela[1], C. Romero-Molina[2], E. Sanchez-Mejias[1], A. Gomez-Arboledas[1], C. Nuñez-Diaz[1], V. Navarro[2], M. Vizuete[2], J.C. Davila[1], J. Vitorica[2], A. Gutierrez[1]

[1]Dept. Cell Biology, Faculty of Sciences, University of Malaga/IBIMA/CIBERNED, Malaga, ES
[2]Dept. Biochemistry and Molecular Biology, Faculty of Pharmacy, University of Sevilla/IBIS/CIBERNED, Seville, ES

Amyloid-beta (Abeta) peptide deposits and hyperphosphorylated tau protein (phospho-tau) accumulate in Alzheimer's disease (AD) brains. These abnormal protein aggregates leads to glial activation, synaptic dysfunction, neuronal loss and cognitive decline. While microglial response has mostly been analyzed in relation to Abeta accumulation, little is still known about inflammatory processes associated with tau pathology. Microglial reactivity and defective glial responses have been involved in these proteinopathies. Our aim is to clarify the effects of Abeta and tau separately, in order to improve the comprehension of their differential contribution to neuroinflammation and neurodegeneration. We compared the progression of these processes in an amyloidogenic AD model (APPSL/PS1M146L) and two different models of tauopathy (ThyTau22 and hP301S) from 2 to 18 months of age. Accumulation of aggregated proteins was assessed using specific anti-Abeta and phospho-tau antibodies. Inflammatory response was studied using a battery of microglial markers (Iba1, CD45, CD68, Trem2 and Gal-3). In the hippocampus of these models, Tau and Abeta pathologies initiated as early as 2 months of age and increased progressively with aging. Neuritic plaques induced a strong microglial activation associated to plaques in APP/PS1 mice. Interestingly, inflammatory markers and microglial reactivity were barely increased in the hippocampus of ThyTau mice in contrast to not only APP/PS1, but also to P301S mice, which displayed a prominent microglial response. Deciphering the specific effects of Abeta, tau and their different toxic species, would indeed enable the development of novel therapeutic strategies and drugs targeting neuroinflammatory pathways related to these proteinopathies.

Acknowledgement

Supported by PI18/01557 (AG) and PI18/01556 (JV) grants from ISCiii of Spain co-financed by FEDER funds from European Union, and by grant PPIT.UMA.B1.2017/26 (RS-V).