INVOLVEMENT OF DIFFERENT Aβ-ASSOCIATED MYELOID POPULATIONS IN THE HUMAN ALZHEIMER'S BRAIN

Marina Mejias-Ortega[1,2], Elisabeth Sanchez-Mejias[1,2], Clara Muñoz-Castro[2,3,4], Laura Trujillo-Estrada[1,2], Marisa Vizuete[2,3,4], Javier Vitorica[2,3,4], Antonia Gutierrez-Perez[1,2]

[1]Facultad de Ciencias, Universidad de Málaga, IBIMA, Dpto. Biología Celular, Genética y Fisiología, Malaga, Spain, [2]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, CIBERNED, Malaga, Spain, [3]Facultad de Farmacia, Universidad de Sevilla, Dpto. Bioquímica & Biología Molecular, Sevilla, Spain, [4]IBiS-Hospital Universitario Virgen del Rocío CSIC, Sevilla, Spain

Parenchymal microglia, the brain-resident immune cells, have been postulated as a critical factor in Alzheimer´s disease (AD) since the identification of genetic risk factors related to their functions. Though the role of microglia in the AD progression/development is still unknown, a dysfunctional response has recently gained support. However, the different phenotypes and the implication of others myeloid cells in the human pathology have not been determined yet. In this work, we analyzed the phenotypic profile displayed by damage-associated myeloid cells in two AD vulnerable brain regions, the frontal cortex and hippocampus. For this purpose, immunohistochemistry and image analysis approaches have been carried out in postmortem brain samples from patients with AD (Braak V-VI stage) and aged controls without neurological symptoms (Braak 0-II stage). Damage-associated microglial cells were clustered around amyloid plaques and expressed Iba1, CD32,TMEM119, CD68,Trem2 and CD45high. A subset of these cells also expressed ferritin and Gal-3. However, and even though some Braak II individuals accumulated reactive CD45 and CD68-positive plaques, only AD patients exhibited parenchymal infiltration of CD163-positive monocyte-derived cells that invaded plaque near blood vessels. While the frontal cortex showed strong microglial activation similar to that reported in amyloidogenic mice, the hippocampus of the same patients showed an attenuated microglial activation with a degenerative phenotype. These results reveal the co-existence of distinct myeloid populations associated with amyloid plaques during disease progression, as well their region-specific contribution to neuroimmune protection. These findings open the opportunity to design targeted therapies, not only to microglia, but also to the population of macrophages to modulate amyloid pathology and provide a better understanding of the immunological mechanisms underlying AD progression.

Supported by ISCiii grants (PI21-0915 (AG), PI21-00914 (JV)); FEDER funds from European Union, by Junta de Andalucia grants (P18-RT-2233 (AG), US-1262734 (JV)); Programa Operativo FEDER 2014-2020, and by grant PPIT.UMA.B1-2019-07 (ESM).