00336 Mouse and Human Microglia Phenotypes in Alzheimer's Disease Are Controlled by Amyloid Plaque Phagocytosis Through Hif1a

Gabriel Chew[1], Enrico Petretto[1], Jose Polo[2], Alexandra Grubman[2], Choo Xin Yi[2], John Fengcong Ouyang[1], Sun Guizhi[2], Nathan Croft[2], Fernando Rossello[2], Rebecca Simmons[3], Sam Buckberry[3], Dulce Vargas Landin[3], Jahnvi Pflueg[3], Teresa Vandekolk[2], Zehra Abay[2], Jonathan Chan[2], John Haynes[2], Sarah Williams[2], Siew Yeen Chai[2], Trevor Wilson[2], Ryan Lister[3], Colin Pouton[2], Anthony Purcell[2], Owen Rackham[1]

[1]Duke-NUS Medical School, [2]Monash University, [3]The University of Western Australia

Aims: The important role of microglia, the brain's resident immune cells, in Alzheimer's disease (AD) is now well recognised, however their molecular and functional diversity, and underlying mechanisms still remain controversial. We aim to not only shed light on the heterogeneity and functions of microglia in relation to ageing and amyloid-beta plaque phagocytosis, but also propose potential perturbagens for manipulating microglial behaviour for AD alleviation.

Methodology: To understand the spatio-temporal and functional differences between plaque-phagocytic and non-phagocytic microglia in AD, we took advantage of in vivo amyloid-beta plaque labelling using a fluorescent dye, Methoxy-XO4. This approach allowed us to map a molecular signature of microglial subsets and to understand their origin and functional properties in AD mice, as well as extending these findings to human AD through generation of the first single cell transcriptome of AD patient brains. In addition, we employed bulk RNA-sequencing, proteomics, and functional validation.

Result: Transcriptomics analysis unveiled independent transcriptional trajectories in ageing and AD. XO4+ microglial transcriptomes linked plaque phagocytosis to altered expression of bona fide late onset AD genetic risk factors. We further revealed that the XO4+ transcriptional program is conserved in human microglia from AD patients and is a direct and reversible consequence of amyloid-beta plaque phagocytosis. Conversely, XO4- microglia in AD displayed an accelerated ageing signature and contained more intracellular post synaptic material than plaque-containing microglia, exposing XO4- microglia as the likely culprits of aberrant synapse elimination in AD, which we confirmed in non-plaque associated microglia in human AD patients. Mechanistically, we predicted HIF1 as a core regulator of the XO4-/XO4+ axis, and further validated the mechanism in vitro using human stem cell-derived microglia like cells.

Conclusion: Together these findings unveiled the molecular mechanism underpinning the functional diversity of microglia in AD, providing opportunities to develop treatments targeted at subset specific manipulation of the microglial niche.