EXPLORING THE IMPACT OF APOE POLYMORPHISM ON THE MOLECULAR, MORPHOLOGICAL AND FUNCTIONAL PROFILE OF iPSC-DERIVED ASTROCYTES FROM ALZHEIMER'S PATIENTS

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Alzheimer's disease (AD) is pathologically characterised by the presence of amyloid-beta plaques, neurofibrillary tangles containing hyperphosphorylated Tau protein, neuroinflammation and neuronal death leading to progressive cognitive impairment. The ε4 allele of the gene encoding apolipoprotein E (APOE), which is mainly expressed in glial cells, is the strongest genetic risk factor for sporadic AD. Increasing evidence has shown that APOE4 may disrupt normal astrocyte activity, potentially contributing to AD pathology, but the impact of different APOE alleles on astrocyte differentiation, maturation and function is not yet fully understood. To go in depth on these questions, we obtained induced pluripotent stem cells (iPSCs) from fibroblasts of AD patients carrying ε3 and ε4 alleles (in homozygosis) and from healthy patients. We also used gene-edited iPSC lines homozygous for the main APOE variants and an APOE knock-out line. iPSC-derived human astrocytes were generated by establishing a differentiation protocol through the consecutive addition of small molecules and growth factors, and the expression of typical markers (GFAP, GLT1, AQP4 and S100beta) and APOE was analysed. In addition, astrocytes exhibited functional features like glutamate uptake capacity and calcium waves production. They also responded to an inflammatory stimulus (IL-1beta and TNF-alpha) or to the presence of amyloid-beta 1-42 peptide by changing their morphology and increasing the expression levels of pro-inflammatory factors and cytokines. Our results shed light on the potential dual role of APOE polymorphism and the individual´s genetic background in favouring or perhaps preventing AD pathology.