Studying sporadic and familial Alzheimer´s disease on iPSC-derived hippocampal and cortical neurons: effect of APOE and Presenilin1

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Sporadic and familial Alzheimer´s disease (AD) are characterized by a progressive neurodegeneration mainly in memory-related areas such as the entorhinal cortex and hippocampus. The epsilon4 allele of gene encoding apolipoprotein E (APOE) is the strongest genetic risk factor for late-onset AD whereas mutations in PSEN1 gene cause early-onset AD. Increasing evidence shows that APOE4 is associated with diverse aspects of AD pathogenesis, but the impact of APOE alleles on neuronal differentiation, maturation and function remains to be fully elucidated. Furthermore, the effect of G206D-PSEN1 mutation on human neurons has been little explored. To clarify these questions, we obtained induced pluripotent stem cells (iPSCs) from fibroblasts of AD patients carrying the epsilon3 and epsilon4 alleles (in homozygosis) or having G206D-PSEN1 mutation, and from healthy patients. We also used gene-edited iPSC lines homozygous for APOE variants and an APOE knock-out line. Both cortical and hippocampal neurons were generated from human iPSCs by establishing differentiation protocols through the addition of small molecules and growth factors, and their cellular, molecular, functional and neuropathological characterisation was performed. iPSCs-derived neurons expressed cortical and hippocampal markers and showed a functional profile determined by glutamate release, electrical activity and synapse formation visualized by electron microscopy. In addition, release of amyloid-beta 42/40, total Tau and phosphorylated Tau to the culture medium, as well as the presence of amyloid-beta plaques and p-Tau181 aggregates are being analysed. Overall, our results point to specific actions of APOE polymorphism and G206D-PSEN1 mutation affecting neuronal differentiation, dysfunction and neurodegeneration.