Elucidating pathways from hereditary Alzheimer mutations to pathological tau phenotypes

https://neurodegenerationresearch.eu/survey/elucidating-pathways-from-hereditary-alzheimer-mutations-to-pathological-tau-phenotypes/

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Institution
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Contact information of fellow
Country

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Elucidating pathways from hereditary Alzheimer mutations to pathological tau phenotypes

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3.4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Alzheimer | neurodegeneration | induced pluripotent stem cell | synaptic connectivity | axon | dendrite | microtubule | short-hairpin screening | tau | neurofibrillary tangles | APP | neurobiology | cell biology

Research Abstract

Alzheimer’s disease (AD) is a fatal neurodegenerative disease, manifested by a progressive loss of synaptic connectivity, neuronal death and memory impairment. AD affects 1 out of 10 Europeans aged over 65. There are no effective therapies for AD, in part because there is no proven molecular explanation of the steps leading from initial neuronal changes to synaptic defects and cognitive consequences.

The two major hallmarks of AD pathology, Abeta plaque deposition and neurofibrillary tangles, arise from increased proteolytic processing of the amyloid precursor protein (APP) and microtubule destabilization due to tau hyperphosphorylation, respectively. Recent data indicates that generation of a beta-C-terminal fragment (b-CTF) of APP acts as a signalling event that induces tau phosphorylation and pathological redistribution of tau from axons to dendrites of neurons. This proposal tests the contribution of proteolytic APP processing, tau phosphorylation and synaptic dysfunction to AD in a human disease-relevant system using neurons generated from human induced-pluripotent stem cells (hIPSC) of AD patients. This hypothesis will be addressed by the following objectives 1) identifying the trafficking and signalling events that control b-CTF to tau signalling 2) define molecular interventions that inhibit b-CTF to tau signalling 3) asses downstream effects of b-CTF induced tau-phosphorylation on tau redistribution, dendritic function and synaptic connectivity.

I will use state of the art microscopy and biochemical analysis combined with a short-hairpin screening approach in established neuronal lines (hereditary AD patient neurons) to identify key pathways involved in abnormal tau phosphorylation, and molecular and electrophysiological techniques to asses dendrite function and synaptic connectivity. This project will contribute to a better understanding of molecular events in AD pathogenesis and will potentially identify novel molecular targets for the treatment of AD.

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