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The dynamic role of human induced pluripotent stem cell derived-astrocyte secreted APOE4 in Alzheimer's disease

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Alzheimer's disease (AD) is the most prevalent neurodegenerative condition worldwide. There are currently an estimated 35 million AD sufferers, and this is expected to double every 20 years so by 2050 there will be round 115 million cases. Late onset AD (>age 65) makes up the majority of cases, and the main contributing factor to the rise in AD is increasing life expectancy. It is well established that the human apolipoprotein E (*APOE*) gene is a strong genetic risk factor for AD, specifically late onset. It encodes one of 3 isoforms *APOE*2, -E3 and -E4, which vary only by 1 or 2 specific amino acids. However, this small change in peptide sequence significantly modifies the protein conformation, and results in isoform specific properties. The end result is that different *APOE* isotypes modify the risk of developing AD. Specifically APOE*4* is associated with an increased risk of AD. In the general population *APOE*3 is the most common allele, and considered the 'normal' version of *APOE*; yet over 65% of AD patients carry a copy of *APOE4*. Furthermore *APOE4*, particularly when homozygous, is associated with a lower age of onset of symptoms, usually 5-10 years compared to the general population. The relationship between *APOE* and AD is mainly attributed to the ability of the *APOE* protein to bind Aβ. Astrocytes, one class of glial cells, are the most abundant cells in the brain. Recent findings are implicating non-cell-autonomous mechanisms of neurodegeneration mediated by astrocytes. Astrocytes are vital for maintaining normal homeostasis for the healthy brain, which is critical for neuronal communication. How astrocyte activities integrate into complex brain functioning, how they respond to insult or injury and whether their responses promote or inhibit repair is poorly understood. Therefore it is critical to understand how to regulate astrocyte function in order to benefit the treatment of neurodegenerative conditions. In our lab, we are addressing the role of *APOE* in AD using human induced pluripotent stem cells (iPSCs) derived from patient donor skin cells; specifically the role of *APOE* in both neurogenesis and astrocytic physiology, with particular focus on astrocytic secreted *APOE*. Primarily, we have compared the effects of the specific astrocyte secreted *APOE* isoform (E4, E3) on health, maturation and physiology of neuronal subtypes that are particularly susceptible in AD. So far, we have found significant differences in the functional properties of iPSC-derived astrocytes using whole-cell patch clamp electrophysiology and calcium imaging, with phenotypic variance amongst the different genotypes (homozygous E3 and E4). Our data revealed a significant decrease of 60% in the sustained component of potassium channel current. This in itself could have significant impact on the ability of astrocytes to efficiently balance ion homeostasis specific to *APOE* genotype. *APOE*s role in clearance of amyloid β (Aβ) in AD is due in part to the physiology of astrocytes, which internalize and degrade Aβ. The altered physiology in our current model could potentially provide a better understanding of *APOE* genotype in health and disease.

Speaker Biography

Talitha Kerrigan is a senior Research associate, Faculty of University of Bristol, UK and She has completed PhD from university of Leeds, UK

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