P001 / #1447

Topic: *Theme A: β-Amyloid Diseases / A1.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

GENOME-WIDE ASSOCIATION STUDIES, FUNCTIONAL GENOMICS AND CELL BIOLOGY IDENTIFY TBC1D5 AS AN ALZHEIMER'S DISEASE-RISK GENE AND UNCOVER ITS ROLE IN OAB CLEARANCE.

Lecture Title:

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Aims: The prevalence of Alzheimer's disease (AD) along with its social and economic burden continues to rise worldwide. Increasing evidence points towards smaller, pre-fibrillary aggregates, known as beta-amyloid oligomers (oAβ), as the primary cause of disease. We identified TBC1D5 as an AD risk gene from multiple resampled GWAS in the Korean population followed by confirmational functional genomic screening in a Drosophila AD model. Further, we investigated the role of this key regulator of intracellular trafficking and vesicle transport in the clearance of oAβ in differentiated neuron-like cells.
Methods: We established a stable cell line lacking TBC1D5 by selectively inhibiting the human orthologue of this endocytic gene using siRNA in differentiated neuron-like SH-SY5Y cells. We then investigated the effect of TBC1D5 knockdown on oAβ uptake, processing and clearance after 3, 24 and 48 hours post-treatment with oAβ.
Results: The levels of TBC1D5 are significantly reduced in the cortex of human AD patients' brains compared to that of age-matched controls and is associated with temporal lobe atrophy. Knockdown of TBC1D5 also increases oAβ accumulation in neuronal-like cells, decreases clearance of oAβ internalised from extracellular milieu and increases Aβ-induced cytotoxicity.
Conclusions: Our results suggest that endocytosis is a major cellular pathway associated with AD, and that down-regulation of molecular components of endocytic machinery may be involved in the pathological mechanisms underlying AD. Modulators of endocytic proteins, like TBC1D5, may serve as effective therapeutic targets to enhance the proper recycling and clearance of toxic oAβ to slow down disease progression.

P086 / #576

Topic: *Theme A: β-Amyloid Diseases / A1.j. Disease Mechanisms, Pathophysiology: Astroglia*

SUITABILITY OF HUMAN-DERIVED CELLS AS A PLATFORM FOR ALZHEIMER´S DISEASE MODELING

Lecture Title:

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Aims: Alzheimer's disease (AD) is characterized by presenting a complex pathology, not fully resolved yet. This fact, together with the lack of reliable models, has impeded the development of effective therapies. Recently, several studies have shown that functional glial cell defects have a key role in the pathology of AD. However, this glial dysfunction, currently, cannot be correctly modeled using the available animal models, so we hypothesized that cells derived from Alzheimer's patients can serve as a better platform for studying the disease. In this sense, human pluripotent stem cells (hPSC) allow the generation of different types of neural cells, which can be used for disease modeling, identification of new targets and drugs development.
Methods: We have a collection of hiPSCs derived from patients with sporadic forms of AD. We have differentiated these cells towards neural lineage to obtain neurons and astrocytes. For the generation of oligodendrocytes (OLs), we have developed a fast and robust protocol to generate mature OLs in just 22 days.
Results: We have generated neural precursors from all the lines tested. In the case of OLs, the cells generated resemble primary OLs and can myelinate neurons in vivo and in vitro using a screening compatible platform. This platform is being transferred for the generation of the other glial cells.
Conclusions: This methodology can be used to elucidate the pathogenic pathways associated with neurodegeneration and to identify new therapeutic targets susceptible to modulation, contributing to the development of new effective drugs against AD.