Synaptic dysfunction in Alzheimer Disease: from new in vitro models to identification of new targets.

https://neurodegenerationresearch.eu/survey/synaptic-dysfunction-in-alzheimer-disease-from-new-in-vitro-models-to-identification-of-new-targets/

Principal Investigators

DILUCA Monica Maria Grazia

Institution

Università degli Studi di MILANO

Contact information of lead PI
Country

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Synaptic dysfunction in Alzheimer Disease: from new in vitro models to identification of new targets.

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The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract

Alzheimer disease (AD) is the most common neurodegenerative disease, which progressively and ineluctably leads to massive brain neuronal death.

A study of the European Brain Council indicated AD among the 12 most costly brain disorders for European society. Accordingly, neurodegenerative diseases -AD in particular- and the search for new treatments represent one of the main priorities in the strategic programs of all member states, including Italy.
In this frame, SynAD involves 8 among the most productive Italian units active in the field of AD and combines their multidisciplinary skills.
The objective of SynAD is to explore novel hypotheses in AD pathogenesis, focusing on the complex interplay between amyloid formation, synaptic failure, inflammation and neuronal death. SynAD will gain new knowledge about AD thanks to:The generation of neuronal precursors derived from AD patients' fibroblasts as a new ad hoc in vitro model. Padovani, Sorbi and Carlesimo Units will collect skin biopsies from AD patients and healthy controls. To obtain neuronal precursors, Sala Unit will re-program collected fibroblast from patients and mice to induced pluripotent stem cells (iPS), that will be differentiated into excitatory neurons. Di Luca Unit will characterize synaptic composition and spine morphology of these iPS-derived neuronal cultures. The identification of new potential targets. We will take advantage of this cutting-edge in vitro model to analyze the crossing pathways of AD pathogenesis, i.e. amyloid cascade, synaptic failure, calcium dependent pathways, inflammation and neuronal death. Di Luca Unit will analyze amyloid cascade components at the synapse, in particular ADAM10, as synaptic element, and its partners, able to regulate its synaptic availability. Hrelia Unit will study Abeta as the driving force for synaptic failure and neuronal death, focusing on activation of cellular and molecular mechanisms of inflammation/death, commanding soluble Abeta-induced neurodegeneration. Canonico Unit will evaluate calcium-dependent gene expression in iPS-derived neuronal precursors and in AD animal models. Carlesimo Unit will collect immune cells (dendritic cells/monocytes) from controls and AD patients. He will analyze their cellular pathways of death, either triggered by soluble Abeta or induced by co-culture with these immune cells in two different models, i.e. neuroblastoma cells and iPS/neuronal precursors.
The characterization of novel biomarkers. We will create a bank of DNA, fibroblasts and cerebrospinal fluid (CSF) obtained from AD patients and healthy controls.
Padovani, Sorbi, Carlesimo and Parnetti Units will be responsible for the enrollment of the subjects and the collection of informed consents and samples. In light of the results obtained from the above described in vitro/in vivo studies, we will evaluate the potential relevance of the identified targets as novel biomarkers of AD. To test these new biochemical clues as potential biomarkers, Padovani and Sorbi Unit will analyze single nucleotide polymorphisms (SNPs) while Parnetti, Padovani and Sorbi Units will evaluate the levels of these proteins in CSF of healthy controls and AD patients in both dementia and pre-dementia stage.
This project takes into account and integrates several pathways interacting in a complex interplay ending in AD pathogenesis. We strongly believe that the proposed multidisciplinary approach might provide critical insights and significant advances in the quest for new strategies for prevention and treatment of AD

Lay Summary
Further information available at:

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Investments > €500k

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