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Conference Abstract

Identification of an Inherent Bioenergetic and Metabolic Phenotype in Late-Onset Alzheimer Disease

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Abstract: The pathology of late-onset Alzheimer disease (LOAD) is still poorly understood, but it is multifactorial and closely related to changes with age. We developed a cellular platform for LOAD collecting skin fibroblasts or blood cells from LOAD patients and non-demented control individuals that are used in the induced pluripotent stem cell (iPSC) paradigm to produce brain cells for determining LOAD pathogenic processes in context of age, disease, genetic background, cell development, and cell type. This model has provided evidence for an innate inefficient cellular energy management in LOAD that is associated with alterations of the cellular transcriptomes and lipid compositions, and interconnected cause-and-effect linkages, such as impaired insulin/IGF-1 signaling, bioenergetic substrate deficiencies, diminished glucose metabolism, disruption of the autophagic flux, and others. In addition, testing of compounds revealed some restoration of the altered bioenergetic and metabolic processes in LOAD cells. Altogether, our studies have identified an inherent LOAD-associated cellular metabolic phenotype as a potential risk factor to develop neurodegenerative disease with age. We propose that our cellular model allows for patient-oriented examination of numerous mechanisms and interactions in LOAD pathogenesis, as a basis for a personalized medicine approach to predict altered aging and risk for development of dementia, and to test or implement (customized) therapeutic or disease-preventive intervention strategies.

Keywords: autophagy; bioenergetics; brain cells; induced pluripotent stem cells; insulin/IGF-1 signaling; late-onset Alzheimer disease; metabolism; neurodegeneration; transcriptome

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