biology and life sciences forum

MDPI

Abstract

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

Kai-Christian Sonntag [1,2,3,*], Woo-In Ryu [1,2,3], Mariana K. Bormann [1,2,3], Eunjung Koh [1,2,3] and Bruce M. Cohen [1,3]

[1] Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, MA 02478, USA; wryu33014@gmail.com (W.-I.R.); mbormann@mclean.harvard.edu (M.K.B.); ekoh@mclean.harvard.edu (E.K.); bcohen@mclean.harvard.edu (B.M.C.)
[2] Basic Neuroscience Division, McLean Hospital, Harvard Medical School, Belmont, MA 02478, USA
[3] Program for Neuropsychiatric Research, McLean Hospital, Harvard Medical School, Belmont, MA 02478, USA
* Correspondence: kai@mclean.harvard.edu
† Presented at Cells, Cells and Nothing but Cells: Discoveries, Challenges and Directions, 6–8 March 2023; Available online: https://cells2023.sciforum.net/.

Abstract: The pathology of late-onset Alzheimer's disease (LOAD) is still poorly understood, but it is multifactorial and closely related to changes with aging. We developed a cellular platform for collecting skin fibroblasts or blood cells from LOAD patients and non-demented control individuals, which are then used in an induced pluripotent stem cell (iPSC) paradigm to produce brain cells for determining LOAD pathogenic processes in the 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 cellular transcriptomes and lipid compositions, and interconnected cause-and-effect linkages, such as impaired insulin/IGF-1 signaling, bioenergetic substrate deficiencies, diminished glucose metabolism, and disruption of autophagic flux, among others. In addition, a testing of compounds revealed some restoration of these 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 for developing neurodegenerative diseases with aging. We propose that our cellular model allows for patient-oriented examination of numerous mechanisms and interactions in LOAD pathogenesis, which can be used as a basis for a personalized medicine approach to predict altered aging and risk of developing 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's disease; metabolism; neurodegeneration; transcriptome

Citation: Sonntag, K.-C.; Ryu, W.-I.; Bormann, M.K.; Koh, E.; Cohen, B.M. Identification of an Inherent Bioenergetic and Metabolic Phenotype in Late-Onset Alzheimer's Disease. *Biol. Life Sci. Forum* **2023**, *21*, 24. https://doi.org/10.3390/blsf2023021024

Academic Editor: Alexander E. Kalyuzhny

Published: 23 March 2023

Author Contributions: Conceptualization, K.-C.S. and B.M.C.; methodology, K.-C.S., B.M.C. and W.-I.R.; validation, K.-C.S., B.M.C. and W.-I.R.; formal analysis, K.-C.S., B.M.C., W.-I.R., M.K.B. and E.K.; investigation, K.-C.S., B.M.C., W.-I.R., M.K.B. and E.K.; resources, K.-C.S. and B.M.C.; data curation, W.-I.R., M.K.B. and E.K.; writing—original draft preparation, K.-C.S.; writing—review and editing, B.M.C.; visualization, K.-C.S.; supervision K.-C.S.; project administration, K.-C.S. and M.K.B.; funding acquisition, B.M.C. All authors have read and agreed to the published version of the manuscript.

Funding: Steele Fund: Program for Neuropsychiatric Research, McLean Hospital (B.M.C.).

Institutional Review Board Statement: The studies were performed in accordance with relevant guidelines and regulations and were approved by the McLean Institutional Review Board (protocol #2007P002597).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the studies.

Data Availability Statement: Data and material are made available upon request.

Acknowledgments: The authors want to thank Suzanne Babb and Fontini Savvides for administrative help.

Conflicts of Interest: The authors declare no conflict of interest.