Aging × Genetics × Environment: Characterization of Precision Disease Models for Preclinical Testing for Late-onset Alzheimer’s disease

Stacey J. Sukoff Rizzo1, Kathryn A. Haynes1, Diogo Francisco S. Santos1, Suzanne Doolen1, Sean-Paul G. Williams1, Gabriela J. Little1, Aman Reddy1, Nicholas Heaton2, Jason T. Hart1, Michael Sasner2, Kevin Kotredes2, Dylan Garceau2, Cynthia M. Ingraham2, Christopher D. Lloyd2, Ravi Pandey3, Christophe Preuss4, Asli Uyar4, Nicholas T. Seyfried5, Paul R. Territo3, Gareth Howell2, Gregory W. Carter2,4, Adrian L. Oblak5, Bruce T. Lamb6, and the IU/JAX/PITT MODEL-AD Consortium

1University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; 2The Jackson Laboratory, Bar Harbor, ME, USA; 3Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, IN, USA; 4The Jackson Laboratory for Genomic Medicine, Farmington, CT, USA; 5Emory University School of Medicine, Atlanta, GA, USA

INTRODUCTION

• The ability to effectively translate therapeutic efficacy from the bench to clinical success for Alzheimer’s disease (AD) has been hampered in part due to limited recapitulation of the complex disease in animal models. While analogous AD risk mutations have been engineered into animal models and have dominated the research field, these have primarily been familial, early onset risk alleles which do not capture the complexity of AD for the majority of patients that present with sporadic late onset AD (LOAD).
• LOAD2 mice exposed to HFD from adolescence (LOAD2+HFD) demonstrated aging changes relative to LOAD2 mice in the absence of HFD on a translational touchscreen task. Intriguingly, gene expression profiles and proteomic signatures of aged LOAD2+HFD mice aligned with ‘omics signatures of AD patients in the absence of core neuritic plaques, which were not detected up to 24 months of age.

METHODS

• Initially, alleles were created using CRISPR to knock-in risk variants to the mouse locus on a sensitized C57BL/6J genetic background expressing APOE4 and Trem2K2529M (LOAD2) see Kotredes et al., 2021, PNAS: 347079460). Later models were made on the same background with a humanized Aβ sequence at P<0.05.
• To investigate the role of high fat diet (HFD) exposure on exacerbating the manifestation of AD related pathologies on aging and genetic risk, we provided HFD ad libitum. Evaluating the contribution of gene expression changes (HFD) in addition to a humanized Aβ sequence at P<0.05. Overall, these studies highlighted the potential for HFD to exacerbate the manifestation of AD related pathologies on aging and genetic risk.

RESULTS

• The IU/JAX/PITT MODEL-AD consortium is focused on developing mouse models with genetic risk variants associated with LOAD, in combination with the ability to effectively translate therapeutic efficacy from the bench to clinical success for Alzheimer’s disease (AD) has been hampered in part due to limited recapitulation of the complex disease in animal models. While analogous AD risk mutations have been engineered into animal models and have dominated the research field, these have primarily been familial, early onset risk alleles which do not capture the complexity of AD for the majority of patients that present with sporadic late onset AD (LOAD).
• LOAD2 mice exposed to HFD from adolescence (LOAD2+HFD) demonstrated aging changes relative to LOAD2 mice in the absence of HFD, including presentation of insoluble Aβ in the absence of a transgenic background. Intriguingly, gene expression profiles and proteomic signatures of aged LOAD2+HFD mice aligned with ‘omics signatures of AD patients in the absence of core neuritic plaques, which were not detected up to 24 months of age.

SUMMARY & CONCLUSIONS

• The biological construct of aging is an essential component for the study of Alzheimer’s disease. Our MODEL-AD approach is to incorporate genetic risk for LOAD, aging, and environmental risk to improve translational relevance of model models for the study of AD.
• LOAD2 mice exposed to HFD from adolescence (LOAD2+HFD) demonstrated aging changes relative to LOAD2 mice in the absence of HFD, including presentation of insoluble Aβ42 in brain and plasma, and increased inflammatory cytokines. 12-month aged LOAD2+HFD mice also demonstrated increased NfL in CSF, as well as vasculature and perfusion changes as measured by MRI. By 18 months, LOAD2+HFD mice demonstrated reductions in hippocampal neurons as well as cognitive impairment relative to LOAD2 mice in the absence of HFD on a transatlantic touchscreen task. Intriguingly, gene expression profiles and proteomic signatures of aged LOAD2+HFD mice aligned with ‘omics signatures of AD patients in the absence of core neuritic plaques, which were not detected up to 24 months of age.

FURTHER INFORMATION

• MODEL-AD: model-ad.org
• AD Knowledge portal: adknowledgeportal.org
• AD Data Explorer: modeladexplorer.org
• TREAT-AD: treatad.org

ACKNOWLEDGEMENTS

MODEL-AD was established with funding from The National Institute on Aging (US4 AG054345).