Journal of Alzheimer's Disease 99 (2024) S183–S185
DOI 10.3233/JAD-240272
IOS Press

Introduction

Omics Approaches in Alzheimer's Disease Research

Sudeshna Das[a,b,*]
[a]*Department of Neurology, Massachusetts General Hospital, Boston, MA, USA*
[b]*Harvard Medical School, Boston, MA, USA*

Accepted 8 March 2024
Pre-press 16 April 2024

With the advent of new omics technologies, in the past few years, there has been a deluge of complex, high-dimensional data on Alzheimer's disease (AD). In particular, single-nucleus technologies have begun to unveil the molecular underpinnings of various brain cell-types and states, their response to AD pathology, and the interactions among them [1]. To date, several bulk and single-nucleus transcriptomics studies on AD have been published that identify cell-specific molecular disruptions observed in AD and the intricate interactions among the various brain cell types [2–5]. In addition, several more studies on proteomics, metabolomics, epigenomics, and genetics have shed light on the complex pathophysiological landscape of AD [6–10]. Moreover, data that shed light on the spatial relationships of brain cells with AD pathology is also being generated [11, 12]. The current supplemental issue is a topical collection to provide new insights into altered pathways and disease-related processes, increasing our understanding of AD pathogenesis to identify specific biomarkers of disease status, progression, or therapeutic response.

The research articles featured in this issue encompass several themes. The first theme is the molecular and cellular mechanisms underlying AD. Chum et al. profile cerebrovascular miRNAs to demonstrate that the gene expression of angiogenesis, vascular permeability, and blood flow regulation families are altered in AD [13]. Another study explored non-coding RNA composition of extracellular vesicles in AD, and report significant differences in miRNAs and tRNAs between AD and controls [14]. A gene co-expression analysis identified multiple AD-related genes that are associated with *FAM222A*, which encodes an amyloid plaque core protein and is an AD brain atrophy susceptibility gene that mediates amyloid-aggregation [15]. Analyzing single-cell omics datasets, Wang et al. found that communication between T cells is weakened in AD patients [16]. Finally, Nelson et al. examined pericytes, which protect against insulin resistance, iron accumulation, oxidative stress, and amyloid deposition, and suggest that pericyte degeneration could contribute to disease progression [17].

The second theme is on biomarkers for diagnosis, prognosis, and drug action. Yan et al. applied machine learning and identified three mitochondria-related genes, NDUFA1, NDUFS5, and NDUFB3, as early diagnostic biomarkers [18]. Sultana et al. investigated the plasma metabolomics profile of older adults with dual-decline in cognition and walking speed, and identified four compounds at higher concentration in dual-decliners compared to non-decliners [19]. Another metabolomics study found accumulation of scyllo-inositol and reduction of hypotaurine

*Correspondence to: Sudeshna Das, PhD, MIND Data Science Lab, 65 Landsdowne St., Cambridge, MA 02139, USA. Tel.: +1 617 768 8254; Fax: +1 617 213 5418; E-mail: SDAS5@mgh.harvard.edu.

as potential biomarkers for AD development [20]. Yet another metabolomics study identified strong inverse associations between medium-chain fatty acids and dicarboxylic acids and global cognition in a Puerto Rican cohort [21]. Weinberg et al. investigated the effect of metformin, an anti-diabetes drug, on plasma and cerebrospinal fluid proteins in non-diabetic patients with mild cognitive impairment and positive AD biomarkers; they successfully identified several putative plasma biomarkers for future clinical trials [22].

The final theme was omics tools and methods that enhance our ability to study AD. Lardelli et al. used zebrafish as a model organism combined with genome editing to study altered gene expression in early onset forms of familial AD (EOfAD) and non-EOfAD-like mutations, and interestingly identified changes to oxidative phosphorylation in EOfAD mutations [23]. Leveraging bioinformatics and electronic structure analyses, Puentes-Diaz et al. assessed the viability of 44 salen-type copper-chelating ligands along with 12 additional proposed compounds for their multifunctional potential in AD treatment [24]. Lastly, Noori et al. developed a freely-available online portal of public omics data for AD researchers to quickly and systematically explore omics datasets to advance AD research [25].

In summary, the major themes across these papers on omics in AD focus on the integration of various omics approaches to understand the molecular basis of the disease, the identification of novel biomarkers for early detection and therapeutic targets, the exploration of the genetic factors contributing to AD risk and progression, and the examination of the role of metabolic alterations in the disease's development. These studies highlight the complexity of AD and the potential of omics technologies to provide insights into its pathogenesis, emphasizing the importance of a multidisciplinary approach to tackle the challenges in diagnosing and treating this condition.

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