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Commentary

Convergent systems-based approaches identify a role for OCIAD1 in Alzheimer's disease

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Alzheimer's disease (AD) affects approximately 30–35 million individuals worldwide, posing a tremendous medical and fiscal burden on society. With life expectancy on the rise, the World Health Organization estimates that the number of people living with AD is predicted to triple by 2050. While its pathogenesis remains elusive, targeting Amyloid β (Aβ) pathology – a hallmark of the disease – in individuals with AD has been a primary focus for industry [1]. Recent failures of clinical trials targeting Aβ have increased the need for a better understanding of AD pathogenesis, particularly its earliest events. Though it is well appreciated that Aβ accumulates in the brains of individuals with AD, the initial consequences of hyperamyloidosis, one of the earliest pathological changes of this disease, remains poorly understood [2]. It is plausible that a better understanding of the earliest phenomena downstream of hyperamyloidosis will help elucidate disease pathogenesis and give rise to novel therapeutic avenues.

There are increasing numbers of transcriptomic and proteomic datasets from both human AD cases and mouse models that can be mined, through bioinformatics followed by functional validation in orthogonal cellular platforms, to yield novel insights into the disease pathogenesis. In this issue of *EBioMedicine*, Li and colleagues contribute to these datasets, devise a pipeline for the identification of novel AD-centric pathways through the integration of multiple "omics" datasets, and elucidate a novel role for OCIAD1 (Ovarian Cancer Immunoreactive Antigen Domain Containing 1) in AD [3]. To begin, they identify key regulatory mechanisms downstream of amyloidosis by performing proteomic assays on two established mouse models of AD, while concurrently comparing gene expression profiles of vulnerable (entorhinal cortex and hippocampus) to less vulnerable (visual cortex) brain regions of sporadic AD patients. The convergence of these datasets yields three factors associated with disease development, one of which, OCIAD1, is upregulated in disease states. In exploring the relationship between OCIAD1 and disease development, Li et al. find that decreasing GSK3β, a key kinase in AD [4], also decreases OCIAD1 levels in cellular models and that, conversely, elevated OCIAD1 levels exacerbate multiple cellular stress responses. Additionally, by examining the protein-protein interaction networks of OCIAD1, they delineate a relationship between BCL-2, OCIAD1, and BAX in mitochondrial-associated neurodegeneration. Together, the authors conclude that OCIAD1 is a novel neurodegeneration-associated factor in the early stages of AD.

Several steps remain before moving this target forward for preclinical trials. First, given that OCIAD1 is ubiquitously expressed throughout the body [5], a careful look at the consequences of its loss in model organisms may shed important light on its native function. Earlier this year, a report suggested that mice lacking *Asrij* (the mouse *OCIAD1* ortholog), are viable and fertile, though progressively accumulate hematological deficits over time [6]. Thus, inhibition of OCIAD1 in humans may require careful regulation in the context of its tissue locale, particularly in the context of an aging population. To wit, a first step forward will be to test whether decreasing *Asrij* is sufficient to mitigate neurodegenerative phenotypes in mouse models of AD. Second, given that a treatment targeting OCIAD1 would be chronic in nature, traditional pharmacology (as opposed to antibody- or antisense oligonucleotide-based approaches) would be a promising approach. As such, it will be critical to identify the specific pathological mechanism of OCIAD1 in order to inhibit its toxicity in AD. Given its potential role in scaffolding proteins as well as regulated mitochondrial metabolism, this may prove to be difficult [7–9]. Alternatively, targeting the regulators of OCIAD1 or its downstream effectors may be additional routes for intervention; though the efficacy of inhibiting targets such as GSK3β while maintaining specificity remains a challenge.

An additional avenue of future investigation will be the use of OCIAD1 as a potential biomarker for AD. Li and colleagues found that OCIAD1 protein levels in the hippocampus correlate with increased pathological staging. To expand on this finding, it will be important to mine the growing body of AD sample/tissue

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repositories (e.g. ADNI, the Alzheimer's Disease Neuroimaging Initiative [10]) to determine if OCIAD1 is found in blood or cerebral spinal fluid and whether changes in its levels correlate with disease status. Using OCIAD1 as an early disease biomarker could help track disease progression and lead to an earlier marker of disease onset to aid in symptom management and future disease-modifying treatment for individuals living with AD.

Declaration of Competing Interest

None declared.

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