Unravelling the molecular landscape of Alzheimer's Disease

Isadora Ferreira

Abstract

Alzheimer's Disease (AD) is characterised by cognitive decline and oxidative stress-related neuronal damage. This study investigated SOD1, an antioxidant enzyme countering reactive oxygen species (ROS), in AD. Brain samples from AD patients and controls were analysed using immunohistochemistry and Western blotting. Results revealed heightened SOD1 expression and activity in AD brains, potentially compensating for increased ROS. Paradoxically, prolonged SOD1 elevation led to hydrogen peroxide accumulation due to imbalanced downstream processing. This study highlights the intricate role of SOD1 in AD-associated oxidative stress. While SOD1 initially counters ROS, sustained elevation can disrupt ROS homeostasis, contributing to neuronal damage. Understanding these complexities offers insights into neurodegenerative disease mechanisms, prompting potential targeted interventions for AD.

Introduction

In the cellular and molecular era of medicine recently, experimental biologists and clinicians aim to understand and influence cell behaviour using focused molecular techniques, such as RNA-sequencing (RNA-seq). To successfully differentiate gene expression alterations between healthy controls and disease subjects, researchers using RNA-seq data, generated by associations, from post-mortem brain tissue samples of Alzheimer's Disease (AD) and healthy individuals, further understand the molecular responsibilities in phenotypic measures of AD.

With the increase in the aging population worldwide, Alzheimer's disease (AD) has become a rapidly increasing public health concern. The relatively uncommon autosomal dominant condition with an early onset, familial AD is triggered by mutations in the genes for presenilin (PRESN1) and the amyloid precursor protein (APP), both of which are involved in the formation of amyloid-beta (Blennow, K *et. al,* 2006), a physiological peptide initiating the degenerative cascade of AD in the brain (Iwata, N *et. al,* 2005). AD is characterised by alterations in the entorhinal cortex and hippocampus (National Institutes of Health, 2017), including conglomerated amyloid-beta plaques, or accumulated hyperphosphorylated tau tangles, resulting in the loss of neurons and the neurotransmitter-mediated connections, and thus, brain atrophy.

The primary application of bioinformatics, is in the field of genomics, which seeks to understand how specific infected tissues' gene regulation contributes to disease development. Gene regulation is the management of the timing, location, and volume of gene expression. It involves switching genes on and off in various patterns depending on the function they serve in the organism.

Methods and Materials

SOD1: Once having attended the SciX Summer School at UNSW, certain articles influenced the specified genomic topic of choice. Although SOD1 was discovered by Rosen and collaborators in 1993 (NCBI, 2022), articles printed in publications such as The Conversation (Crossley, Merlin, 2023), and The Guardian (Cox, David, 2023), allowed for the following investigation to be constructed.

Brain samples:
This investigation in based on secondary data which was collected from post-mortem brain tissue samples. The tissue samples were selected from the CNDR based on the presence of plaques and neurofibrillary tangles within each brain. Gene Set Enrichment Analysis was performed using the genes upregulated or downregulated in AD versus old samples and the gene expression of the same genes in AD after ERCC spike-in normalization.

R Studio:
R Studio was installed via Posit.co for programming. Data was downloaded via EdgeR SupSeries (Nature Genetics, 2020). Functions were downloaded on RStudio (filter.upregulated.genes <- function(data, logfc=0.5, fdr=0.05).
25,000+ gene expression list were condensed in accordance to P-Value, and LogFC to contain >500 genes. Condensed data was placed into Excel to produce a Volcano plot showing the p-value vs. LogFC.

Results

Gene Set Enrichment Analysis (GSEA), was used post RNA-seq and revealed 25,503 differentially expressed genes in which there was data generated from patients with AD (*n= 12),* healthy elder patients (*n=10)* and healthy younger patients (*n=8).* There was a mean age of 68 for AD and elder patients, and 52 for younger (Nativio, R *et. al,* 2018). Genes IGHM and RBM3 were of interest due to their significant nature within patients of AD. By contrasting gene regulation between samples exhibiting and absent of AD, this study was able to discover the phenotype measures of AD.

The volcano plot (Graph 1) shows the upregulation of SOD1 uncovered in this study, has a consequential impact in AD pathogenesis with a $p < 0.05$.

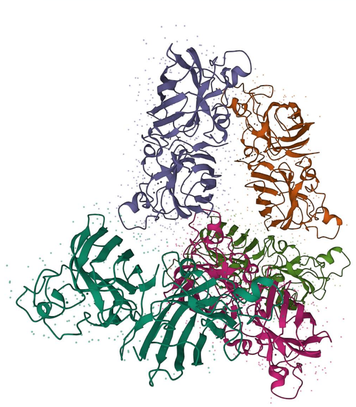


Figure 1. Ribbon model of the Protein structure of SOD1.

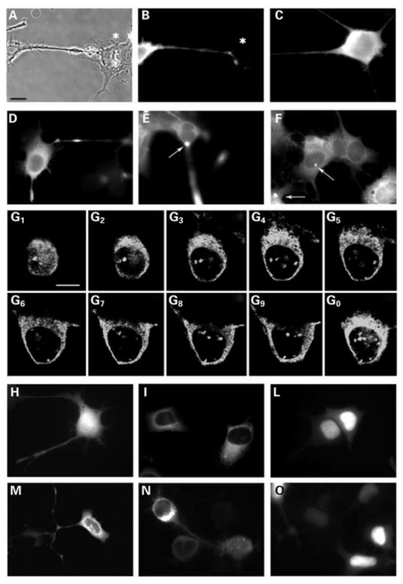
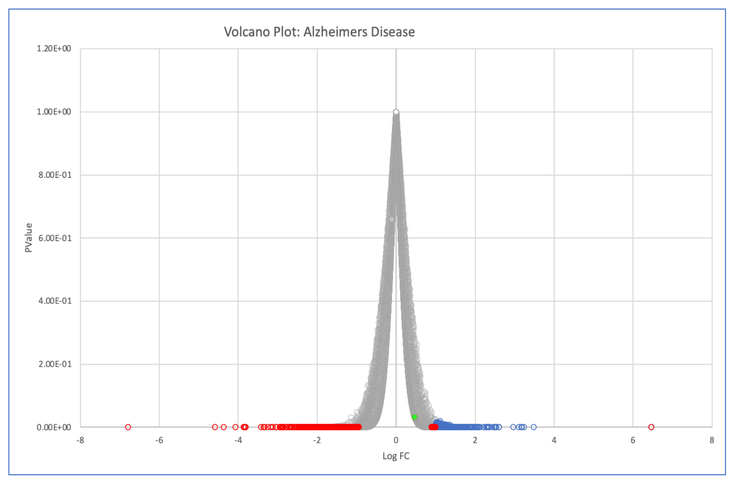


Figure 2. SOD1 in cell body of neuron.



Graph 1. Volcano Plot of AD gene regulation

Gene	LogFC	P-value
RBM3	2.05739969	2.25x10-20
SST	2.52355228	1.45x10-21
RNU11	-2.8573985	2.34x10-22
NPC1L1	-4.5882568	9.94x10-23
FAT2	-2.6637702	5.23x10-26
AL355075.4	-4.369389	1.78x10-29
AP000763.2	3.47491978	3.96x10-31
AL157935.2	-3.3518599	2.79x10-35
IGHM	-6.7853271	5.77x10-36
AL138099.4	6.46033973	1.90x10-94

Table 1. Top 10 most significant genes in AD brain

Discussion

This investigation highlights the crucial role of SOD1 in protecting the brain from oxidative stress and reactive oxygen species (ROS) accumulation, which is relevant to Alzheimer's disease (AD) pathogenesis. Upregulated SOD1 in AD patients partially safeguards against neurotoxicity. A prior study by Murakami and Murata reveals the dangers of SOD1 deficiency in an AD mouse model, leading to amyloid β (Aβ) protein oligomerization and memory loss due to oxidative damage. While SOD1 levels vary between healthy individuals and AD patients, its specific phenotypic role within AD's neurodegenerative context remains understudied. Superoxide radicals, formed during oxygen reactions, contribute to ROS, which, when accumulated, can damage cellular components and induce cell death, including ferroptosis. Mitochondrial dysfunction and lipid peroxidation are implicated in ferroptosis induction. Additionally, SOD1 mutations are linked to familial ALS, impacting nuclear protection. Anderson's study indicates that mutated SOD1's altered solubility might affect cellular health and motor neuron function.

Conclusions

This bioinformatics investigation has unveiled the intricate connection between SOD1 and oxidative stress in AD. Initially, increased SOD1 expression serves as a defence against ROS levels in AD brains. However, a crucial shift occurs, with prolonged SOD1 elevation contributing to hydrogen peroxide accumulation due to disrupted downstream processing. These findings carry significant therapeutic implications, highlighting the need for nuanced strategies targeting AD. Understanding the delicate balance between SOD1 expression and ROS processing offers a potential avenue for interventions that restore equilibrium. Overall, this study acknowledges SOD1's role in AD-related oxidative stress, creating room for more targeted approaches to address this facet of AD pathology.

Contact

Isadora Ferreira
Year 12 Student
Northern Beaches Christian School
Email: 23if@student.nbcs.nsw.edu.au

Acknowledgments

Thank you to:

The UNSW SciX Team
PhD candidate Lachlan Gray
PhD candidate Laurene Leclerc
Mrs. Collins (NBCS Science Extension teacher)

For their continuous support and assistance.