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Short Communication

Cell-type Specific Expression Changes in Aging and Alzheimer Disease

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ABSTRACT

Aging is common to all human organisms. It is a risk factor for neurodegenerative diseases including Alzheimer's Disease (AD). Global bulk gene expression profiling have previously suggested that the disease is governed by diverse transcriptional regulatory networks. Computational analysis of exon microarray/RNA-Seq data may enable detection of involved genes and pathways. Bioinformatic/statistical analyses may identify additional discrete glial, immune, neuronal and vascular cell populations spanning both AD and control post mortem brain samples. Notably, astrocytes and microglia cell gene markers have displayed the greatest transcriptomic impacts, with the induction of both shared and distinct gene program.

Keywords: Aging; Alzheimer's disease; RNA-Seq.

INTRODUCTION

Exon microarray analysis of young and aging samples (1,231 samples, 134 samples 10 brain regions, source: UK brain bank) identified cell type specific gene expression and cell quantities changes in the human brain (e.g. decrease of oligodendrocytes and increase of number of large neurons [1]. More than 6 million Americans of all ages have Alzheimer's. An estimated 6.7 million Americans age 65 and older are living with Alzheimer's in 2023. Seventy-three percent are age 75 or older. About 1 in 9 people age 65 and older (10.7%) has AD. AD single-cell analysis of 2 AD and 2 control post mortem brain samples identified changes in microglial and astrocyte marker genes [2]. Previous studies identified several genes and pathways involved in AD but many are still unknown [3]. In addition the role of amyloid β, diverse intracellular processes and neuronal cell-types are likely required for Alzheimer's progression. Non-neuronal genes (e.g. microglia, MG markers) have been shown to have a central role in Alzheimer's pathology, as exemplified by Genome-Wide Association Studies (GWAS) with associated variants having largely glial cell restricted expression. Furthermore, it is becoming increasingly clear that signals from the central nervous system are required to sustain microglial cellular specification. Notably, loss of those cues dramatically disrupts the microglia phenotype driving them toward an activated cellular state.

Aims and objectives of the study

The specific objectives of my study were:

- To detect genes which show expression changes in Aging and AD.
- Detect Aging and AD involved molecular pathways.

METHODS

In the studies, I have employed sophisticated statistical/bioinformatic and computational analyses for the analyses of microarray and RNA-Seq datasets. These included t-test, ANOVA, Hierarchical Classification (HCL) PCA and t-sne. All the data was deposited under the GEO and is available for download (accession number GSE175814), link https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?).

RESULTS

I surveyed gene expression differences in over 25,000 single-nuclei collected from the brains of two Alzheimer's disease (AD) patients in Braak stage I and II and age- and gender-matched controls hippocampal brain samples. Apolipoprotein E (APOE) status was not measured for this study samples (as well as CERAD and THAL scores). Additionally, I previously analysed

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AD Vacht model mice RNA-Seq data and detected altered genes and molecular pathways [4,5].

DISCUSSION AND CONCLUSION

The studies opens new venues for better understanding of molecular mechanisms that underlie aging/AD. Specifically, they reveal potential involvement of cell-type specific genes in AD. They may open new venues for future therapeutics of AD. Currently there are also developments of blood-based test for early detection of AD which seems very promising.

Microarrays and RNA-Seq studies may enable us to better understand genes and pathways involved in aging and AD. Specifically, neuronal and microglial cell-type specific genes. Future studies may enlarge the cohort sizes and generate mice organism models for comparison. Moreover, the results may also be compared to analysis results of Parkinson's patient's blood leukocyte RNA based on RNA-Seq data analysis as there might be common genes and pathways altered in both AD and PD .

ETHICAL STATEMENT

All the Alzheimer's and control samples have approved signed MTA (number T61.16 AND TR73.16) from the university of Edinburgh (e.g. curtesy of Mrs. Chris Ann McKenzie and Prof. Colin Smith) dated 25/11/2016 (given under supplementary information). This specific study was reviewed and approved by an institutional review board (ethics committee) before the initiation of the study.

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