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Multi-Omics Database-Driven Discovery of Alzheimer's Disease Biomarkers and Risk Factors

Yassel Yu

K. International School Tokyo, Tokyo, Japan
yasselyassel@icloud.com

Abstract. Recently, Alzheimer's disease (AD), as one of most prevalent neurodegenerative disorders, has emerged as the main diseases affecting the elderly. It induces progressive memory loss, cognitive decline, and hippocampal atrophy, leading to the decline of the quality of individual's life and casing the burden of society. This problem of widespread dementia is not a temporary one either, but one that would have growing impacts as societies around the world begin to age. Although amyloid PET imaging and CSF biomarkers (e.g., Aβ42, p-tau, total tau) can be the diagnosis markers for the detection of AD pathology, non-invasive methods for the detection of AD at the early stage are still unclear. The breakdown of the blood-brain barrier (BBB) has been proved as an early event in AD pathogenesis. Neutrophils, as key cells in the process of inflammation, infiltrate brain tissue following BBB breakdown, exacerbating neuroinflammation and neuronal apoptosis. Several studies have identified the neutrophil-related biomarkers (e.g., NGAL, MPO, and NLR) for AD diagnosis, indicating that the blood-based biomarkers related to neutrophil dysfunction offer a promising approach for early AD detection. However, these current biomarkers can not cover all the diagnosis of early AD development. Therefore, herein this study, by integrating multiple human and mouse single-cell RNA sequencing (scRNA-seq) datasets about blood neutrophils for BBB functions, we selected the 17 high potential biomarkers from more than 2,000 genes for blood neutrophil dysfunctions and BBB breakdown, we identified genes as potential non-invasive biomarkers for the early diagnosis of AD. By conducting such a study and identifying neutrophil-related transcripts across species, we aim to contribute to the development of a non-invasive, scalable approach to AD detection that could be implemented on large-scale screenings.

Keywords: Alzheimer's Disease, Biomarker, Blood-Brain-Barrier, Blood neutrophil, Inflammation, scRNA-seq

1. Introduction

The global population, particularly in developed countries, is undergoing a demographic shift toward aging. Among the elderly, Alzheimer's disease (AD) has emerged as one of the most prevalent neurodegenerative disorders. As of 2021, dementia affects approximately 57 million individuals worldwide, with AD accounting for over 60% of cases. Projections indicate an annual increase of 10 million cases [1]. The economic burden is substantial, with global dementia-related

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costs exceeding 1.3 trillion USD annually as of 2019. This figure is expected to rise as populations age, making dementia an increasingly pressing global challenge. AD, the leading cause of dementia, can cause irreversible neurodegeneration and progressive clinical decline, ultimately resulting in patient mortality. Clinically, AD manifests through progressive memory loss, cognitive decline [2], language impairments (e.g., word-finding difficulties, discourse incompleteness), and behavioral changes [3-5]. Currently CSF biomarkers (e.g., Aβ42, p-tau, total tau) [6,7] are used to predict cognitive decline and neuropathology at autopsy [8] for the early AD detection. While CSF biomarkers are valuable for AD detection, their limitations—cost, invasiveness, sensitivity gaps, and stage/ethnicity-dependent variability—highlight the need for complementary approaches (e.g., plasma biomarkers) to improve early and accurate diagnosis [9-11].

Pathologically, AD is characterized by the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) in the brain, both of which disrupt neuronal function and synaptic integrity [12,13]. Importantly, the blood-brain barrier is a highly specialized vascular structure that maintains brain homeostasis by selectively regulating molecular exchange between circulation and the central nervous system. Blood-brain barrier disruption occurs in the early stages of Alzheimer's disease [14], even accelerating clinical symptoms by the infiltration of peripheral immune cells [15]. Emerging blood-based biomarkers (e.g., MMP-9, GFAP, and neurofilament light (NFL) [16,17] can detect BBB dysfunction before amyloid pathology develops [18], indicating this non-invasive and effective blood test for identifying AD risk in its earliest stages, potentially reshaping diagnostic paradigms and therapeutic strategies.

Neutrophils, as key mediators of inflammation, play important roles in AD progression through their interactions with the BBB. After BBB leakage, neutrophils infiltrate brain tissue and exacerbate neuronal apoptosis and neuroinflammation [19]. Elevated neutrophil-lymphocyte ratio (NLR) in blood correlates with AD pathology, though its specificity is debated due to comorbidities [20]. In addition, several studies have identified the neutrophil -related biomarkers (e.g., NGAL, MPO, and NLR) [21] for the confirmation of AD. These findings indicated that blood-based biomarkers reflecting neutrophil dysfunction may offer a promising approach for early AD detection. However, the neutrophil biomarkers for diagnosis of AD pathology at early stage are still unclear.

In this study, we propose utilizing multi-omics bioinformatics approaches to characterize neutrophil-derived molecular signatures associated with BBB dysfunction in AD. Through systematic integration of transcriptomic data and proteomics, we aim to establish neutrophils as a novel, non-invasive peripheral biomarker for early disease detection.

2. Method

2.1. Data collection

We retrieved four single-cell RNA sequencing (scRNA-seq) datasets from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo) related to Alzheimer’s disease (AD) and neutrophil activity in both human and mouse models. The datasets included the following GEO accession numbers: GSE226602, GSE255662, GSE211099, and GSE263094.

Among these, GSE226602 and GSE255662 contain blood-derived neutrophil transcriptomic data from human and mouse samples, respectively. GSE226602 comprises 11,394 cells (4,706 from AD samples and 6,688 from controls), while GSE255662 includes 33,489 cells (17,118 from AD model mice and 16,371 from control groups).

The remaining datasets, GSE211099 and GSE263094, consist of scRNA-seq data from mouse brain samples under inflammatory conditions. In these studies, control groups received phosphate-

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buffered saline (PBS) injections, whereas experimental groups were treated with lipopolysaccharide (LPS) to induce neuroinflammation mimicking AD pathology using the wild-type mouse. We categorized each group as either "PBS" or "LPS" and merged the two datasets (GSE211099 and GSE263094) to generate a unified mouse brain dataset for downstream analysis.

2.2. Data pre-processing and integration

For the preparation of each dataset, we firstly combined these datasets using the functions like FindIntegrationAnchors and IntegrateData and harmony were performed using default parameters to correct the batch effects. Then, we performed quality control (QC) to ensure quality of data for downstream analysis. The cells with more than 5% mitochondrial genes and double cells will be excluded to remove any dead cells or double cells contained within the data. The cell numbers in each treatment after QC and the grouping information are shown in Figure 1. Then, the neutrophils in each sample will be extracted using neutrophil specific markers.

2.3. Identification of differentially expressed genes and volcano plot

To identify differentially expressed genes (DEGs) in treatment vs control group, we firstly isolated the neutrophils from each dataset and then the FindMarkers (https://satijalab.org/seurat/reference/findmarkers) was conducted to analysis the DEGs, using the selective parameter log-fold change (logFC) > 0.5 and adjusted p-value < 0.05. By using this function, we obtained a list of DEGs. The significantly up-regulated and down-regulated DEGs were visualized by using a volcano plot.

2.4. Enrichment analysis

The identified DEGs were conducted the analysis of Kyoto Encyclopedia of Genes and Genomes (KEGG) (KOBAS) and GO biological process (GOBP) using EnrichR (https://maayanlab.cloud/Enrichr/enrich), with significance levels determined by adjusted p value <0.05 to show the functional and pathway enrichment of these DEGs.

2.5. UMAP and violin plot

Uniform manifold approximation and projection (UMAP) was used to visualize the clusters and cell distributions of neutrophils by reducing dimension. Then a violin plot was used to show the gene expression level of patients and control samples in human blood neutrophils.

3. Results

3.1. Data integration and extraction of neutrophils from the combined datasets

Previous studies have proved that BBB breakdown occurs at the early stages of AD pathology [22], and neutrophils are highly associated with the inflammatory storm after infiltration into the BBB. We thus hypothesize that identifying functional changes of neutrophils at early stages of AD pathology may be helpful for the development of biomarkers for early diagnosis. Therefore, we selected AD-related scRNA-sequencing data from the GEO database, including human blood samples (GEO226602), mouse blood samples (GEO255662), and brain samples with LPS-induced AD pathology (GEO211099 and GEO263094). Through the analysis of DEGs from each dataset, the

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overlapped DEGs are considered as the potential key modulators for neutrophils' functions in AD pathology by regulating integrity of the BBB.

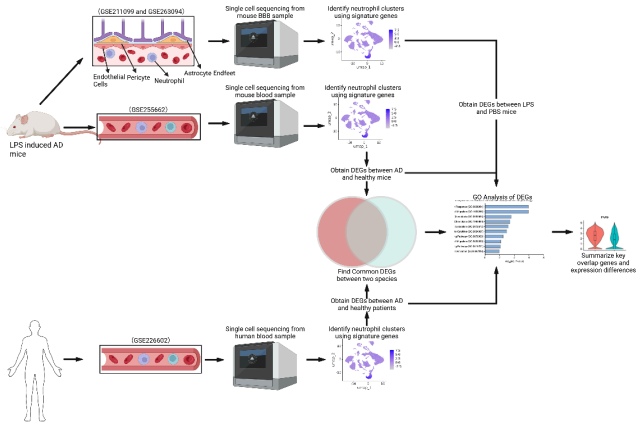


Figure 1. Diagram for data processing

To explore the functional changes of neutrophils in AD pathology, we first integrated each scRNA-seq sample in every dataset by Seurat. After QC and extraction of neutrophils using the neutrophil-specific markers (such as Lyz, S100a9, Fcgr3, and Prtn3) shown in Figure 2, we obtained 74670 neutrophils from these datasets in total, then unsupervised grouped by the UMAPseparately. By using UMAP, we can visualize how the cells between the two groups differ through the distribution of clusters, from which we can make quick observations on whether differences exist between the two groups.

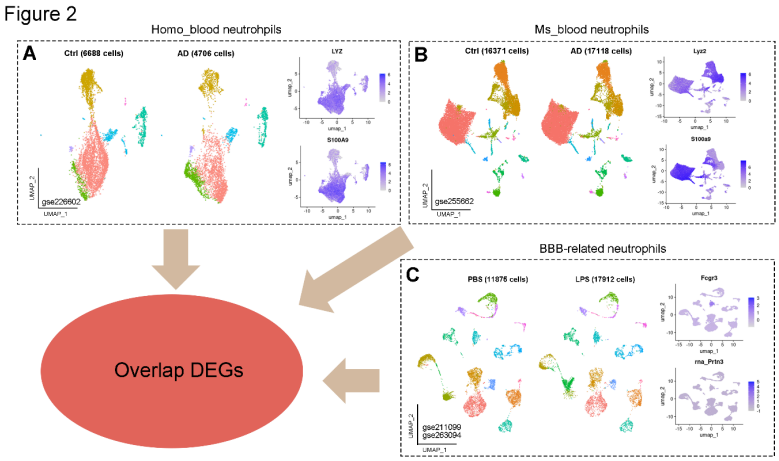


Figure 2. UMAP clustering of cells and labelling of common genes

UMAP clustering of Human Blood neutrophils (GSE226602) and labelling of common neutrophil genes on clusters, with 6,688 neutrophils from healthy patients (Ctrl, left) and 4,706 cells from AD patients (AD, right). (B) UMAP clustering of Mouse Blood neutrophils (GSE255662) and labelling of common neutrophil genes on clusters, with 16,371 neutrophils from healthy mice (Ctrl, left) and 17,117 neutrophils from AD mice (AD, right). (C) UMAP clustering of BBB neutrophils

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(GSE211099 and GSE263094) and labelling of common neutrophil genes on clusters, with 11,876 neutrophils from mice treated with PBS (PBS, left) and 17,912 neutrophils from mice treated with LPS (LPS, right).

3.2. The DEGs analysis

In the extracted neutrophils, the significantly changed DEGs were analyzed and then showed by the volcano plot in Figure 3-5. Among them, in human blood neutrophils, the top DEGs enriched in the functions are shown to be related to cell migration and cell adhesion in Figure 3B by GOBP analysis (e.g., Regulation of Actin Cytoskeleton Organization (GO:0032956)). The KEGG analysis results shown in Figure 3C further suggested the enriched pathways of these DEGs for immune response and cell adhesion (e.g., TGF-beta signaling pathway, focal adhesion) [23]. These results indicated that at the early stage of AD development, the enhanced migration ability of neutrophils showed the recruitment from the peripheral to the BBB. In mouse blood neutrophils, the sharply enriched pathways associated to inflammation (e.g., TNF signaling pathway) suggested their increased neuroinflammation tendencies for regulating AD pathology [24] in Figure 4B, 4C. Additionally, in mouse BBB-related neutrophils, we also observed the enriched functions of inflammation and cell migration in Figure 5B and 5C. All these results demonstrate that, during early stages of AD, the neutrophils that infiltrate into BBB may be responsible for BBB breakdown and that genes with altered expression may be the candidate indicators for diagnosis.

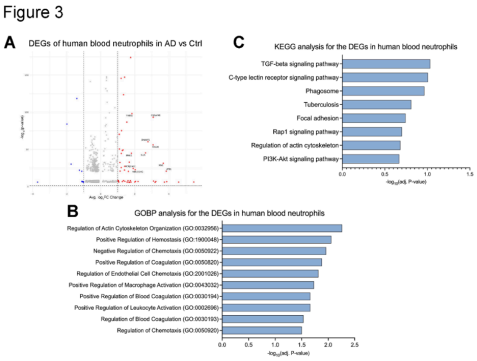


Figure 3. DEGs in AD patient vs Healthy patient blood neutrophils and analysis

(A) Volcano plot for DEGs of human blood neutrophils (GSE226602). (B) GOBP analysis results for human blood neutrophils. (C) KEGG analysis results for human blood neutrophils.

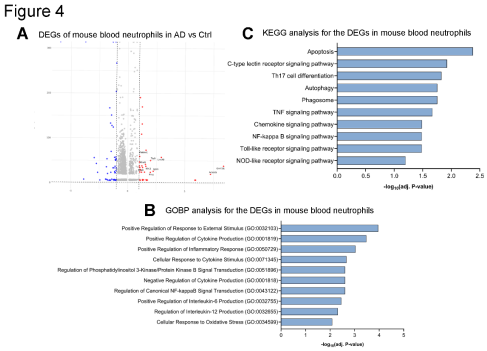


Figure 4. DEGs in AD vs Control mouse blood neutrophils and analysis

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(A) Volcano plot for DEGs of human blood neutrophils (GSE255662). (B) GOBP analysis results for mouse blood neutrophils. (C) GOBP analysis results for mouse blood neutrophils

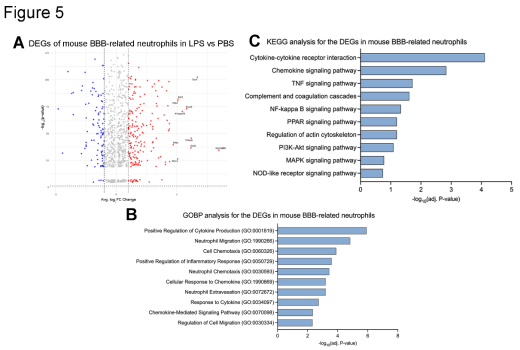


Figure 5. DEGs in LPS vs PBS mouse BBB neutrophils and analysis

(A)Volcano plot for DEGs of human blood neutrophils (GSE211009 and GSE263094). (B) GOBP analysis results for human blood neutrophils. (C) KEGG analysis results for human blood neutrophils.

To further confirm the genetic changes for neutrophil functions, we merged the DEGs in the blood neutrophils (217 genes) in both the human and mouse dataset and BBB-related neutrophils (2059 genes) to obtain the 33 overlapped genes in Figure 6A. The functional and pathway analysis in Figure 6B and 6C suggest that the multiple functions and pathways activated that relate to neutrophil activation, immune response and cell migration. Therefore, this functional analysis suggested that the neutrophils infiltrated into the BBB have pro-inflammatory properties for promoting BBB breakdown and AD development.

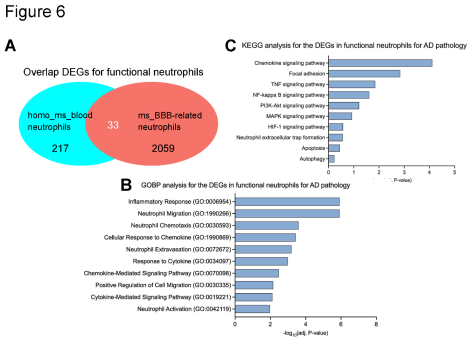


Figure 6. Overlapping DEGs and their analysis

(A) Venn diagram showing overlap of DEGs between human and mouse blood neutrophils (homo_ms_blood neutrophils, 217 DEGs, left), mouse BBB-related neutrophils (ms_BBB-related neutrophils, 2059 DEGs, right), and overlapping DEGs (33, middle). (B) GOBP analysis results for overlapping DEGs from intersection of part a. (C) KEGG analysis results for overlapping DEGs from intersection of part a.

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3.3. Neutrophil biomarkers for early detection of AD

To further uncover the potency of identified DEGs for AD diagnosis, we linked the expression level of these genes and their molecular functions. As shown in Figure 7, we identified upregulated DEGs (e.g., CCL3, CD83, CYTIP, ClEC4E, G0S2, IL-1β, LYZ, PDE4B, and THBS1), and downregulated DEGs (e.g., EGR1, FOS, IQGAP2, IFITM1, FGL2, KLF2, IFITM2, S100A11, and PLAC8) in infiltrated blood neutrophils. We selected these genes from the total of 33 overlap genes in Figure 6. because they are the ones we found to be most relevant to neutrophil functions. The graphs that are displayed in Figure 7 are selected as the ones that show changes, as the ones not listed did not display visible violin plots suitable for visualization. The upregulated DEGs like IL-1β, CCL3, and LYZ contribute to neutrophil activation and proinflammatory response. Especially, the genes of IL-1β and CCL3 are responsible for the recruitment of blood neutrophils [25,26].

A

DEGs			
Gene	Avg. Log2FC	Gene	Avg. Log2FC
CCL3	1.341875	FGL2	-0.3509754
CD83	0.7395822	KLF2	-0.3478589
EPS8	-0.1984293	IFITM6	NA
ATF3	0.5176408	FDPS	-0.2021429
CYTIP	0.2369611	IFITM2	-0.3102449
DHRS9	1.038604	IFIT3	-0.3436347
CLEC4E	0.4787416	LYZ	0.4372837
CCL5	0.6865338	H2-AB1	NA
EGR1	-0.6508202	IFI207	NA
G0S2	1.0924262	IFIT3	NA
FOS	-0.609553	MS4A4A	-0.72418
IQGAP2	-0.3235346	S100A11	-0.1501061
IFITM1	NA	PDE4B	0.7969578
IFITM3	0.2294095	PLAC8	-0.392471
IFI211	NA	THBS1	1.8295473
IL1RN	0.7665491	SLFN5	-0.3649473
IL1B	1.5311697		

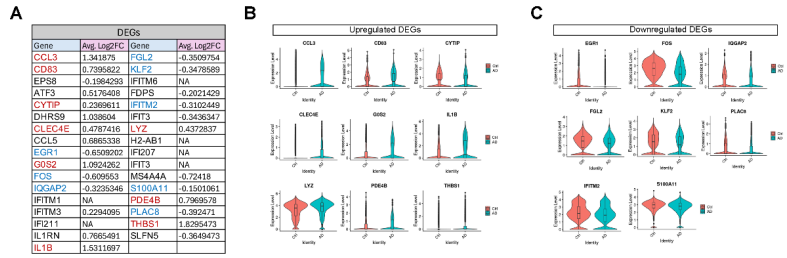


Figure 7. Table of overlapped DEGs and violin plots

(A) Table showing overlapping differentially expressed genes between control group and AD group, with up-regulated genes included in part b shown in red and down-regulated genes included in part c shown in blue. (B) Violin plot showing up-regulated genes, with the red violin on the left showing neutrophil gene expression in the control group (ctrl) and the blue violin on the right showing neutrophil gene expression in the AD group (AD). (C) Violin plot showing down-regulated genes, with the red violin on the left showing neutrophil gene expression in the control group (ctrl) and the blue violin on the right showing neutrophil gene expression in the AD group (AD)

Most importantly, in the human blood proteomics analysis, the protein level of CCL3 was also upregulated in patients, strongly indicating its potency as the biomarker. The increased level of G0S2 is key for the metabolic reprogramming, which may support the survival of neutrophils under the immune microenvironment [27,28]. This gene is usually responsible for modulating the cell cycle, restricting lipid droplet release (affecting energy production), and affecting inflammatory signaling in immune cells such as the neutrophil [29]. Given G0S2's role in inhibiting lipolysis, its reduced expression may facilitate the energy mobilization necessary for enhanced chemotaxis and inflammatory function at the blood–brain barrier. PDE4B can promote the inflammasome activation and pyroptosis after LPS induction [30] and impose the dysfunction of glucose metabolism [31]. Interestingly, while THBS1 protein, an important gene for blood vessel generation [32], is downregulated in late stage of AD patients, its increased mRNA level at the early stage may reflect BBB breakdown, with potential to be a biomarker of neutrophils.

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In addition, as shown in Figure 7C, the downregulated genes, including EGR1, FOS, S100ALL, and PLAC8, are also related to the immune functions of neutrophils. IQGAP2, as the modulator for cellular cytoskeletons, can regulate the cell mobility of blood neutrophils.

Taken together, we highlighted the potential importance of genes like CCL3, IL-1β, THBS1 for the potency of non-invasive biomarker for AD diagnosis at early stages, although further experimental confirmation may be needed to confirm the practical applications of diagnosis using these biomarkers.

4. Discussion

In this work, we identified the prevalence of up-regulation of chemokine and adhesion process related genes in neutrophils of both human AD patients and mouse models. Through DEG analysis, we discovered the common tendency of neutrophils to have increased cytokine, chemokine, and cell migration related gene expression in AD patients, AD mice, and LPS-induced mice when compared to control. In the GO enrichment analysis conducted on mouse neutrophils, an abundance of "cytoplasmic translation," "macromolecule biosynthetic process", and "gene expression" genes were observed along with a parallel to human results, sharing similar processes such as leukocyte activation and chemotaxis regulation being increased in AD patients. KEGG analysis further highlights chemokine signaling and focal adhesion pathways, indicating increased inflammation responses and neutrophil migration. When viewed along with BBB inflammation, this KEGG result suggests neutrophil migration relation with BBB breakdown. Additionally, one of the most significant DEGs found during DEG analysis was cd83, a regulator in immune responses to inflammatory disorders. In an article published by Iking-Konert in 2002 [33], it was found that the expression of CD83 in neutrophils was a major contributor to chronic inflammatory disease, which is much like the case of BBB inflammation found in AD, suggesting that neutrophils may in fact have a long-term effect on BBB inflammation, reinforcing its position in AD pathogenesis as a potential cause instead of an emerging symptom.

The coordinated up-regulation of chemotactic and adhesion genes in AD neutrophils suggests that these cells have increased inflammation and migration responses. The intersection of neutrophil between mice and humans especially demonstrates inflammatory and migration responses, which likely reflect the readiness of neutrophils to synthesize cytokines and adhesion factors, all of which contribute to neutrophil driven inflammation in both species. Notably, a previous study [34] also identified a similar DEG of CCL2 being up-regulated in neutrophils, which Zhang's team speculated it to be associated with AD progression due to its pro-migratory nature.

While this study offers various innovative insights into neutrophil-related changes in AD, several limitations should be acknowledged to contextualize these findings. For one, while batch effect correction steps were implemented in the data processing pipeline, the varying experimental conditions under which different sources conducted their experiments under could still have residual effects to influence gene expression patterns. Additionally, due to the scope of this study, no experimental validation of analyzed DEGs and related markers was performed. Therefore, it cannot be confirmed that the observed transcriptomic changes will be translated to neutrophil-caused BBB dysfunction in-vivo. Future studies should aim to validate the identified neutrophilic biomarkers, such as using immunohistochemistry or integrating proteomic or ELISA to provide a more comprehensive view of neutrophil activity in AD pathology. Despite these limitations, though, the findings presented here offer a potential path for subsequent studies and may contribute to the identification of early immune biomarkers for Alzheimer's disease.

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5. Conclusion

In summary, by using transcriptomics data collected with single cell sequencing, we identified DEGs from human AD patients, AD mouse models, and from mice with LPS-induced BBB breakdown. We found that these groups share common GOBP and KEGG processes concerned with cytokine synthesis and focal adhesion. Additionally, we also identified common DEGs across groups, including ones such as CD83, IL-1β and CCL3, all of which are pro-inflammatory and the former especially playing a significant role in chronic inflammation, revealing them to be important potential non-invasive biomarkers for AD diagnosis at early stages. Our findings unveil the similarity in neutrophil function between human AD patients and mice, but more importantly identifying DEGs and processes that underlie neutrophil caused inflammation in AD and its potential role in early AD progression, offering an innovative perspective on the role of neutrophils on AD pathogenesis.

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