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Brain Endothelial Cell Expression in Alzheimer's Disease Showing Stage-Associated Changes

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Abstract

Alzheimer's disease (AD) is the most common type of dementia. Brain endothelial cells (BEC), as an important component of the blood-brain barrier, play a significant role in the pathogenesis of AD. Based on the human brain data provided by Allen Brain Map, this study used two programming systems, Python and R, to investigate the expression characteristics of BEC in the progression of AD and their relationship with different pathological stages. We observed significant expression differences in BEC at certain pathological stages. We further introduced gender as a biological variable and established a linear regression model to evaluate whether there were differences between genders. The results showed that the slopes of BEC expression changes in men and women were slightly different, but there was no statistically significant difference. Furthermore, gene differential expression analysis revealed that compared with the No Dementia group, the BEC in the Dementia group had many genes with significant expression changes, and these genes affected multiple biological pathways. In conclusion, this study has depicted the preliminary characteristics of cerebrovascular endothelial changes in patients with AD from the perspectives of cell quantity and transcription, and provided new clues for the study of the vascular mechanism of AD.

Keywords

Alzheimer's Disease, Endothelial Cells, Gene Expression, Neuropathological Stages

1. Introduction

AD, the most common dementia, accounts for 60 to 80 percent of all dementia cases [1]. Its incidence rate increases with age. With global aging, it is estimated that there will be approximately 140 million people suffering from AD by 2050 [2]. AD can cause memory loss, cognitive impairment, disarray of movements and other symptoms by destroying neurons, and eventually lead to the death. There are two pathological characteristics of AD, accumulating of amyloid beta (Aβ) outside neurons and tangling of tau protein within neurons. The amyloid cascade hypothesis holds that the accumulating of Aβ outside neurons is an inducer of AD [3]. Several papers point that the accumulating of Aβ is mainly caused by defects in the Aβ clearance system rather than excessive production of Aβ [4]-[6].

Blood-brain barrier (BBB) is the largest site for substance transport and exchange in the brain, which plays a significant role in the transport of Aβ [7]. There are multiple carrier proteins in the BBB capable of transporting Aβ, and low-density lipoprotein receptor-related protein-1 (LRP1) and receptor for advanced glycation end products (RAGE) are two of the most important [8]-[12]. LRP1 can transfer Aβ from the brain into the blood through mediating endocytosis, thereby achieving the purpose of Aβ clearance [9] [10]. However, RAGE binds to Aβ and stimulates various cellular responses, which leads to the transfer of Aβ from the blood to the brain and causing Aβ accumulation [11] [12]. BEC are the main cells that constitute the BBB and are also one of the primary expression cells of the above two Aβ carrier proteins [13] [14]. BEC can also take Aβ into the cells through endocytosis and energy-dependent pathways and degrade it in acidic organelles [15].

Some studies have shown that the number of BECs in AD patients changes [16]. Aβ can cause oxidative stress through a series of reactions, which overly increases the expression of vascular endothelial growth factor, leading to abnormal angiogenesis [17]. Additionally, cerebral hypoxia and inflammation can also activate angiogenesis [18]. Some studies suggest that Aβ promotes extensive neovascularization, resulting in increased vascular permeability and subsequent vascular proliferation in AD [19]. These studies all indicate an increase in the number of BECs in AD. The vascular hypothesis, however, posits that the number of BECs decreases in AD [20] [21]. Meanwhile, studies have also shown that Aβ can inhibit the migration and proliferation of BECs [22]. Aβ also accumulates in blood vessels. The accumulation of Aβ on the outer membrane of blood vessels has an anti-angiogenic effect, which may lead to the reduction in the number of BECs observed in AD patients [23].

Given the inseparable connection between BEC and AD, it is necessary to further explore the relationship between BEC and AD. This study, based on the human brain data from Allen Brain Map, integrates the quantitative changes of endothelial cells with the pathological stages of AD, while considering gender as a biological variable. We also explore the difference of gene-level expression changes of BEC between AD samples and non-AD samples. Hoping this study can

provide a new perspective on the vascular pathological mechanism of AD.

2. Materials and Methods

2.1. Data Source

The data used in this paper is from Allen Brain Map. We utilized the Donor metadata and AD data from this website. This dataset is based on post-mortem brain tissue samples from humans and encompasses detailed neuropathological features and cell type expression profiles. There are total 65 available samples in the dataset, including 26 male samples and 39 female samples; 32 samples are classified as dementia and 33 as no dementia according to Cognitive Status.

2.2. Python Data Analysis

The original data was preprocessed and preliminarily analyzed using the Python environment, Jupyter Notebook. Screen all samples and remove the unavailable sample data. The Python libraries used in the analysis include but are not limited to pandas, numpy, and matplotlib.

To explore the effect of AD on cell expression, samples were divided into two groups, "high-level" and "low-level", based on AD-related pathological indicators (such as Braak, LATE, Overall AD neuropathological Change, etc.). For example, samples with Braak II were defined as the "low-level" group, while those with Braak VI were defined as the "high-level" group. The T-test was used to conduct statistical analysis on the cell expression levels of the two groups (with the significance level set at $p < 0.05$), in order to screen the cell types with significant differences in expression. Cell types with significant differences were combining the stage indicators such as Braak, LATE stage, Overall AD Neuropathological Change, and Thal of the samples, the linear regression equations of the cells at different stages were drawn. To observe the dynamic changes of cells during the AD process.

To further explore the influence of AD on cell expression, the samples were divided into two groups, "male" and "female". The linear regression equations of cell expression in two groups at different pathological stages were respectively plotted in the same figure. The two linear regression equations were statistically analyzed using the T-test, and the significance level was set at $p < 0.05$.

2.3. R Data Analysis

RStudio was used to conduct the difference analysis of gene expression data, and create a volcano plot to more intuitively display the significance and degree of change of gene expression differences. The R language packages used include ggplot2, Seurat, dplyr, ggrepel, and *et al.*

Use RStudio to read the data related to endothelial cells in all samples and integrate them in one file. All samples were divided into two groups, "no dementia" and "dementia", according to the Cognitive Status of the samples. Calculate the expression Fold Change (log2 Fold Change) and the significance of difference (p-

value) of each gene respectively. Draw a map of the volcano to visually display the log2 Fold Change and significance level of differentially expressed genes (upregulated if the log2 Fold Change is > 0.6; downregulated if log2 Fold Change is < 0.6; p value < 0.05). Mark the names of the top ten most prominent genes in the figure.

All genes with significant expression differences in "Dementia" were listed, and placed in ShinyGO 0.82 to detect which cellular functions these genes would affect.

3. Result

3.1. AD Leading to Differences in Cell Expression

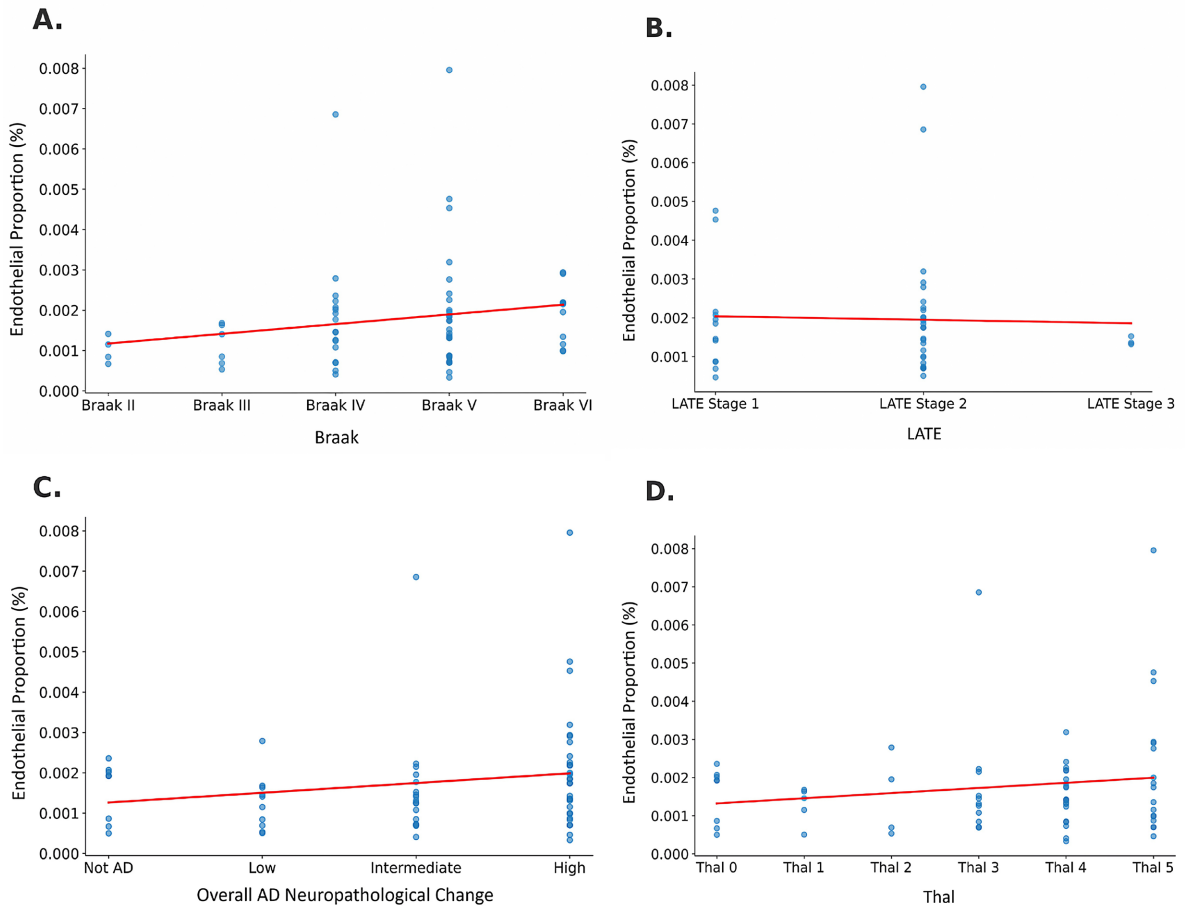

Figure 1. Endothelial cell expression across AD pathological stages. A-D demonstrated the expression changes of endothelial cells in different pathological stages of AD through linear regression analysis. Including (A) Braak; (B) LATE; (C) Overall AD Neuropathological Change; (D) Thal. Each dot represents one sample.

The analysis results indicated that some cells showed significant differences in cell expression between the "high-level" and "low-level" groups ($p < 0.05$). For example, endothelial cells showed differences in Braak II and Braak VI ($p = 0.04645$) (Figure 1A). Since endothelial cells have been found to be correlated with AD in previous studies, this study mainly focuses on endothelial cells. Further, the linear regression plots drawn based on pathological stages such as Braak, LATE, Overall

AD Neuropathological changes, and Thal presented the dynamic change trend of endothelial cell expression with the aggravation of AD pathological stages (Figure 1). However, there were no significant differences in endothelial cells in the groups of other pathological stages except Braak ($p > 0.05$). To clarify the correlation between the pathological process of AD and the expression level of endothelial cells, we further calculated the Pearson correlation coefficient between cell expression and pathological grade. The results indicated that endothelial cells showed a weak correlation with Braak and Overall AD Neuropathological changes ($r = 0.1996$, $r = 0.1892$), but it was not statistically significant ($p = 0.1109$, $p = 0.1312$). Other pathological grades did not show any correlation with endothelial.

Red lines indicate linear regression trends across stages. The X-axis represents pathological stages, and the Y-axis represents the proportion of BEC to the total number of cells. Only in (A) Braak was a significant difference in endothelial cell expression observed (Braak II vs. Braak VI, $p = 0.04645$), while no significant difference was observed in the other pathological stages ($p > 0.05$). Further Pearson correlation analysis showed that There was A weak correlation between endothelial cells and (A) Braak ($r = 0.1996$, $p = 0.1109$) and (C) Overall AD Neuropathological Change ($r = 0.1892$, $p = 0.1312$). But none of them had statistical significance. No correlation was found in the remaining pathological stages.

3.2. No Significant Sex Differences in AD-Associated Endothelial Expression Changes

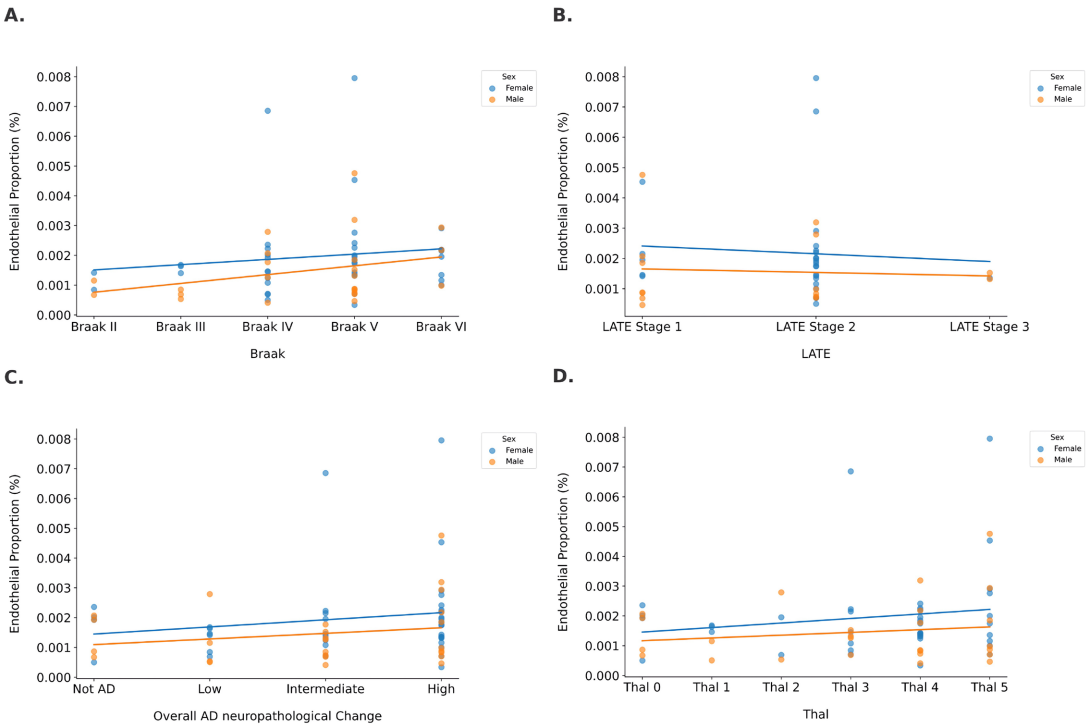

Figure 2. Sex has no significant effect on the abundance of endothelial cells in AD pathological stages. A-D respectively present the changing trends of endothelial cell abundance by gender in different AD pathological stages. Including (A) Braak, (B) LATE, (C) Overall AD neuropathological Change, (D) Thal.

To further explore the influence of gender on the expression of endothelial cells in the pathological process of AD, we took gender (male and female) as the grouping variable and conducted hierarchical regression analysis on the relationship between the expression level of endothelial cells and pathological stage indicators respectively. A linear regression model including gender interaction terms with Braak, LATE, Overall AD Neuropathological Change and Thal as pathological indicators (Figure 2). The summary showed that none of the models demonstrated that gender would affect the expression changes of endothelial cells (Table 1).

Each dot represents a sample and the blue and orange regression lines correspond to the female and male groups respectively. The X-axis represents pathological stages, and the Y-axis represents the proportion of BEC to the total number of cells. The analysis results show that gender does not lead to differences in endothelial cell abundance in AD pathological stages.

Table 1. Linear regression results of four pathological indicators of AD.

Pathological Stage	Sex	Regression Slope	p-value	R^2	Significant
Overall AD Neuropathological Change	Female	0.0002	0.255	0.064	×
	Male	0.00015	0.874		
Braak	Female	0.0002	0.402	0.065	×
	Male	0.0003	0.713		
Thal	Female	0.0002	0.263	0.060	×
	Male	~0.00014	0.768		
LATE	Female	−0.0003	0.712	0.041	×
	Male	−0.0002	0.878		

Grouped by gender, show the changing trends of endothelial cell expression under the four pathological indices of Braak, Thal, LATE, and Overall AD neuropathological Change.

3.3. Genetic Differences between Dementia and No Dementia

To determine the differences in endothelial cell gene expression between dementia patients and no dementia control group, we used the volcano plot to show the significance of the differentially expressed genes and the amplitude of expression changes (Figure 3). The red dots represent genes that are significantly upregulated in the dementia group, the blue dots represent genes that are significantly decreased in expression in the dementia group, and most genes that do not show significant changes are presented as gray dots. Among the genes with significant differential expression changes, we marked the top ten genes with the greatest expression changes among the up-regulated genes and the down-regulated genes.

The significance and expression variation range of differentially expressed genes were demonstrated by drawing volcano maps. The horizontal axis repre-

sents the average expression Fold Change (avg_log2 FC), and the vertical axis represents -$\log_{10}$ (p value). The red dots represent significantly up-regulated genes (avg_log2 FC > 0.6 and $p < 0.05$), the blue dots represent significantly down-regulated genes (avg_log2 FC < −0.6 and $p < 0.05$), and the gray dots represent genes with no significant difference. The figure shows ten up-regulated and ten down-regulated genes each with the greatest expression changes to highlight the representative variations.

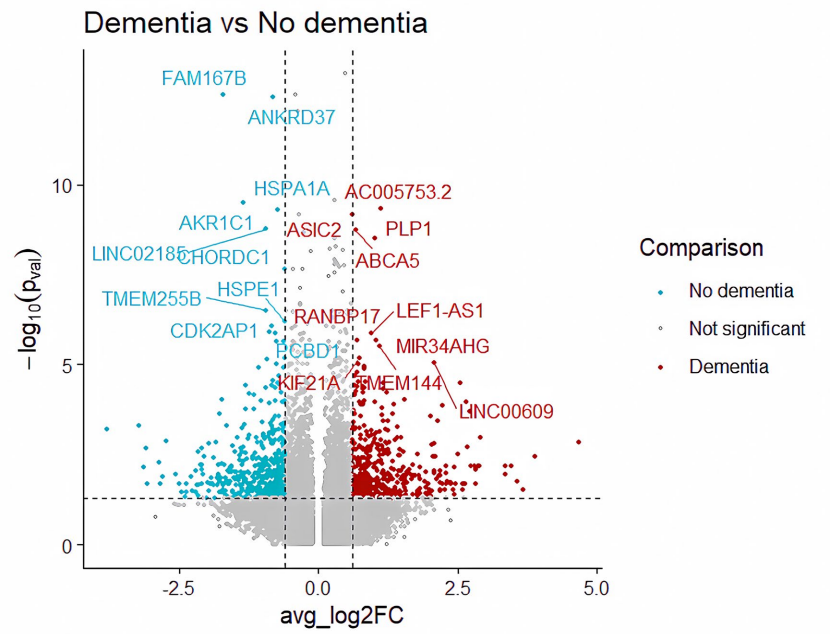

Figure 3. Volcano map of differentially expressed genes of endothelial cells between the dementia and no dementia groups.

3.4. Dementia Group Upregulates Gene Enrichment in Neuro-Related Biological Processes

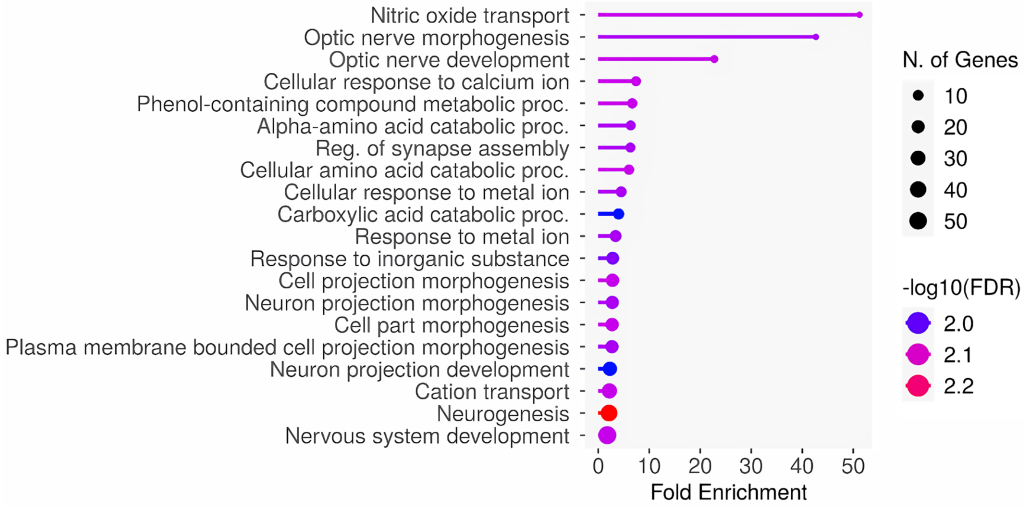

Figure 4. GO biological process enrichment analysis of upregulated genes in the dementia group.

To explore the biological functions of upregulated genes in BEC from the dementia group, GO Biological Process enrichment analysis was performed using ShinyGO. The analysis results show that these upregulated genes are significantly enriched in multiple biological processes related to neural development and neural structure remodeling (**Figure 4**). The functions with a relatively high enrichment multiple include Nitric oxide transport, Optic nerve morphogenesis/development and Cellular response to calcium ion. Furthermore, a large number of genes are involved in neurosystem-related pathways such as Neurogenesis, Neuron projection development and Nervous system development. Among them, the number of upregulated genes enriched by Neurogenesis was the largest, and it had the lowest FDR, showing the highest statistical significance. These results reveal that the changes in endothelial cell expression may not only reflect alterations in the vascular system but also be closely related to neurological abnormalities.

4. Discussion

Based on the AD data from Allen Brain Map, this study investigated the expression of endothelial cells in AD patients at different pathological stages and further evaluated the gender differences and changes in gene expression. Although the analysis did not show strong statistical significance, it still revealed some notable biological trends and potential clues.

We found that the expression levels of endothelial cells only differed in the "high-level" and "low-level" groups of Braak. The Pearson correlation coefficient also showed that there was only a weak correlation between endothelial cells and multiple pathological indicators of AD, and the correlation coefficient was relatively low. It did not reach statistical significance in the linear regression analysis either. Moreover, current studies have contradictory evidence regarding whether the vascular density of AD patients increases or decreases [24]-[27]. It has been shown that high physiological concentrations of Aβ monomers induce angiogenesis by blocking the processing of Notch intermediate NEXT by γ-secretase and reducing the expression of downstream Notch target genes [26]. In addition to Aβ, overexpression of Tau also leads to increased total vessel density in the cortex [25]. However, some studies have shown that the presence of Aβ induces BEC apoptosis [27] [28]. Consistent with these observations, although the research results indicated a subtle difference in the number of BEC between the high-level and low-level Braak groups, this did not strongly support the pure angiogenesis or degenerative model, and there was no statistical difference in the research results of other AD pathological indicators. These results suggest that the pathological progression of AD may not be achieved through linear changes in endothelial cell expression in a single dimension, reflecting that the role of the vascular system in AD may be more complex, possibly involving nonlinear mechanisms, multiple regulatory pathways, or being disturbed by multiple factors such as brain regions, cell types, and individual differences. The data results of this study cannot resolve this debate.

Put significantly upregulated genes in the endothelial cells of the Dementia group into ShinyGO, and functional enrichment analysis was conducted based on the GO Biological Process database. The figure shows the top several significantly enriched biological processes ranked by enrichment multiple. The size of the dots indicates the number of genes involved in the biological process, and the color indicates statistical significance ($-\log_{10}$(FDR)). The significantly enriched biological processes include nitric oxide transport and optic nerve morphogenesis /development. Biological processes involving more genes include nervous system development, neuron projection development, and neurogenesis. The analysis results indicate that the transcriptional changes of endothelial cells in the Dementia group may be closely related to neurological abnormalities.

A large number of studies have shown that gender affects the incidence of AD [29] [30], and that women are more severely affected by AD than men [31] [32]. At the genetic level, loss of CD2AP enhances the vascular toxic effects of Aβ, and this is more pronounced in male mice [33]. Female carrying the APOE4 allele are more likely to be diagnosed with AD than men carrying this gene [34] [35]. These findings suggest that gender may lead to differences in the expression of endothelial cells in patients with AD. However, in the gender analysis of this study, we did not observe a significant gender moderating effect. Although there are slight differences in the regression slopes between men and women, they do not reach the significant level. This result may imply that the impact of AD on the cerebrovascular system is roughly similar in both male and female.

The expression levels of many genes are altered in BEC of AD patients [16]. In addition to the previously mentioned CD2AP and APOE4, RAGE also has increased expression of CCR5 in BEC [36] [37]. However, the expression levels of LRP1 and P-gp are decreased [38]-[40]. In the differential expression analysis of genes in this study, we found that there were significant expression differences in endothelial cells between the dementia and no dementia groups. However, among the top ten most expressed genes in the Dementia group, the AD-related genes mentioned in the previous literature were not detected. This might be because the expression of these genes varies greatly among different cell types. For instance, APOE4 is expressed more frequently in astrocytes but less frequently in BEC [41]. However, these new differentially expressed genes still provide potential clues for the vascular pathological mechanism in AD.

While the analysis of endothelial cell quantity revealed only weak and non-significant differences between AD pathological stages, the gene expression analysis provided strong and statistically significant results. This contrast highlights that vascular alterations in AD may not primarily manifest as changes in the total number of brain endothelial cells, but rather as shifts in their molecular and functional states. Gene expression data capture subtle regulatory and pathological changes—such as endothelial activation, dysfunction, or altered signaling pathways—that may not be reflected in cell abundance alone. Together, these complementary analytical perspectives suggest that the vascular role in AD involves com-

plex molecular reprogramming rather than straightforward cell loss or proliferation.

Past studies have shown that the nerves of AD patients are greatly affected. The enrichment analysis results of ShineGO in this paper provide strong evidence for this. The analysis results showed that the BEC upregulated genes of AD patients were significantly enriched in multiple neuro-related biological processes, including neurogenesis, neuron projection development and nervous system development. Among them, neurogenesis has the highest enrichment significance and the largest number of involved genes. This phenomenon may reflect a compensatory neurogenesis response triggered by the body to resist nerve damage caused by AD. This speculation is consistent with the existing research results that the expression of marker proteins of immature neurons does increase in the hippocampal tissue of AD patients [42].

Furthermore, the results also showed that pathways such as nitric oxide transport and cellular response to calcium ion had a relatively high enrichment multiple, indicating that nitric oxide and calcium ions could have an impact on AD. This supports that cellular calcium homeostasis disorder plays an important role in the pathogenesis of AD [43], and the chronic absence of NO in endothelial cells may lead to Aβ-related pathological and cognitive decline [44]. These results support that BEC may mediate the AD process through the neurovascular pathway. These functional enrichment results have strengthened the signals revealed by differential expression analysis from a biological perspective, providing a new entry point for understanding the interaction mechanism between the vascular system and the nervous system in AD.

This study found that there was a certain relationship between AD and the expression of endothelial cells, but the overall correlation was weak and did not reach a statistically significant level. Although previous studies suggested that CD2AP deletion and APOE4 might play differential roles between genders, these two genes were not found in the differential expression analysis of the genes. Moreover, no significant interaction was found in the gender analysis, indicating that under the current data conditions, the effect of AD on endothelial cell expression is roughly similar between men and women. The analysis of differential expression of genes revealed potential candidate molecules. Between the Dementia and No Dementia groups, multiple genes with significant expression differences were identified. These newly identified genes provide new candidate targets for AD-related vascular lesions.

Although this study provides certain preliminary evidence, there are also some important limitations. Firstly, the sample size is relatively limited. Especially after grouping, it may reduce the efficiency of model checking. Secondly, we failed to distinguish between brain regions or the microenvironment and were unable to capture region-specific expression differences. Thirdly, the cross-sectional data adopted in this study cannot yet reflect the dynamic change process of a single sample over time. These limitations may reduce the ability to detect known AD-

related signals, especially if their changes are subtle or region-specific.

In conclusion, although no strong statistical association was found in this study, the obtained results provide preliminary clues to the cerebrovascular mechanism of AD. Future studies can combine larger sample sizes, multi-omics data (such as single-cell transcriptomes, spatial transcriptomes, genotype information), and brain region-specific analyses to further explore the regulatory mechanisms of endothelial cell changes in AD and their gender dependence, and promote the development of precise intervention strategies.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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