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Original Article

Comparison of Cerebral Cortex Transcriptome Profiles in Ischemic Stroke and Alzheimer's Disease Models

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Conflict of Interest
The author declares that they have no competing interests.

ABSTRACT

Ischemic stroke and Alzheimer's disease (AD) are representative geriatric diseases with a rapidly increasing prevalence worldwide. Recent studies have reported an association between ischemic stroke neuropathology and AD neuropathology. Ischemic stroke shares some similar characteristics with AD, such as glia activation-induced neuroinflammation, amyloid beta accumulation, and neuronal cell loss, as well as some common risk factors with AD progression. Although there are considerable similarities in neuropathology between ischemic stroke and AD, no studies have ever compared specific genetic changes of brain cortex between ischemic stroke and AD. Therefore, in this study, I compared the cerebral cortex transcriptome profile of 5xFAD mice, an AD mouse model, with those of middle cerebral artery occlusion (MCAO) mice, an ischemic stroke mouse model. The data showed that the expression of many genes with important functional implications in MCAO mouse brain cortex were related to synaptic dysfunction and neuronal cell death in 5xFAD mouse model. In addition, changes in various protein-coding RNAs involved in synaptic plasticity, amyloid beta accumulation, neurogenesis, neuronal differentiation, glial activation, inflammation and neurite outgrowth were observed. The findings could serve as an important basis for further studies to elucidate the pathophysiology of AD in patients with ischemic stroke.

Keywords: Ischemic stroke; Dementia; Middle cerebral artery occlusion; 5xFAD model; RNA sequencing

INTRODUCTION

Ischemic stroke is a leading cause of global mortality [1] and can also result in disability and reduced quality of life [2]. It is characterized by brain infarction caused by the occlusion of cerebral blood flow [3,4] and is also correlated with the onset of dementia such as Alzheimer's disease (AD) [5,6].

AD has several hallmarks, including excessive deposition of amyloid beta, neuronal intracellular neurofibrillary tangles, and neuronal loss in cognition related brain regions such as the hippocampus and cortex [7,8].

The incidences of stoke and AD are simultaneously increasing internationally [9,10]. A recent meta-analysis identified the concurrent increase in the number of patients with stroke and AD [11]. A previous study demonstrated that over 80% of patients with AD experienced ischemic stroke caused by amyloid deposition in cerebral blood vessels [12]. Furthermore, a study demonstrated the high risk of AD onset in an ischemic stroke model with cerebral amyloid angiopathy [13].

Considering previous reports, dementia appears to share common risk factors with stroke [14] and leads to increased risks for death following ischemic stroke [15-18].

A recent clinical study reported that mortality after ischemic stroke increased with the onset of AD [19]. Several studies have reported that stroke can cause dementia accompanied by cognitive impairment, neuronal cell damage, mitochondrial dysfunction, and glia activation [20-25]. Although there is much evidence on the relationship between ischemic stroke and AD, the genetic mechanisms shared between 2 diseases are not completely understood. In this study, I compared the cerebral cortex transcriptomes from middle cerebral artery occlusion (MCAO) mice, a mouse model of ischemic stroke [26], with those from 5xFAD mice, an AD mouse model [27]. I identified that the function of commonly altered RNAs was associated with neuronal cell death, glia inflammation, and synaptic dysfunction in AD and ischemic stroke brains. These findings are thought to provide important basic data for broadening the understanding of the AD-like neuropathology in ischemic stroke patients by understanding the effect of RNA commonly expressed in both diseases.

MATERIALS AND METHODS

Data used to analyze the transcriptome of 5xFAD and MCAO mouse models

To compare the common transcriptomic profile between MCAO mouse brain cortex and 5xFAD mouse brain cortex, I obtained RNA sequencing data from the cerebral cortex of 8-month-old male 5xFAD mice from the Gene Expression Omnibus (GEO) database with the accession number of GSE168137 [28]. I also obtained RNA sequencing data from the cerebral cortex of 3-month-old male ischemic stroke MCAO mice (GSE137482) [1].

Analysis of RNA sequencing data

The RNA sequencing data obtained from the ischemic stroke and AD models were screened for low-quality sequencing reads using Trimmomatic [29] (**Figure 1A**). The trimmed sequences were matched to the mouse genome (mm10) using the spliced transcript alignment to a reference aligner [30]. The Cuffnorm value was used to examine normalized values of fragments per kilobase of transcript per million mapped reads (FPKM) based on the GENCODE annotation (Release M17, GRCm38.p6 [31]) (**Figure 1A**). Transcripts with an average FPKM value of < 1 or transcripts not detected in any sample were excluded from additional analysis (**Figure 1A**). A t-test was used to sort transcripts with a significantly different expression between MCAO and 5xFAD groups. The commonly altered mRNAs between the cortex of MCAO and 5xFAD groups were selected for further functional analysis.

Functional analysis of mRNAs

For the functional analysis, significant expression changes based on a p value of ≤ 0.05 were selected in the MCAO and 5xFAD groups. Among them, the commonly changed genes with the same direction in the MCAO and 5xFAD groups were chosen. This filtering resulted in

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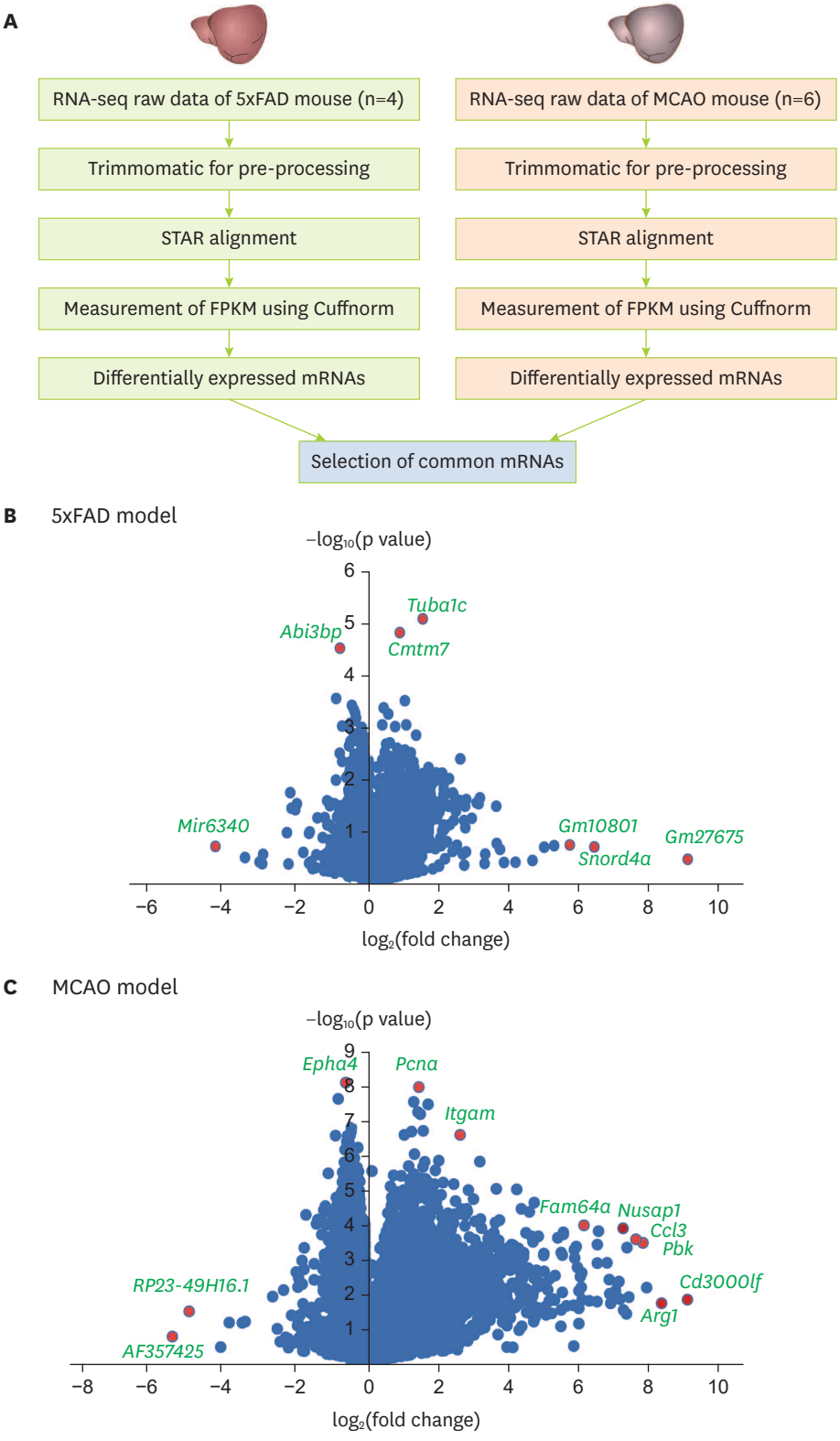

Figure 1. Analysis of transcriptomic data from the brain cortex of MCAO and 5xFAD mouse models. (A) Analysis of transcriptome data. Volcano plots of (B) the 5xFAD group and (C) the MCAO group. The X-axis represents the $\log_2$-transformed fold change in both the groups, and the Y-axis represents the $-\log_{10}$(p value) value. Red dots show significantly altered genes.
MCAO, middle cerebral artery occlusion; STAR, spliced transcript alignment to a reference; FPKM, fragments per kilobase of transcript per million mapped reads.

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231 significantly increased genes and 128 significantly decreased genes in both groups. These 359 genes as common genes in both groups were used for the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis and gene ontology (GO) analysis with the Molecular Signatures Database [32]. For the same group of genes, functional annotation clustering was conducted using the Database for Annotation, Visualization and Integrated Discovery (DAVID) clustering tool [33].

RESULTS

The transcriptome data from 4 5xFAD model brain cortex and 6 MCAO brain cortex were analyzed. For the RNA sequencing analysis of cerebral cortex from 8-month-old 5xFAD mice, data from the publicly available dataset of the GEO database (GSE168137) were analyzed. For the RNA sequencing analysis of cerebral cortex from 3-month-old MCAO mice, the data from the publicly available dataset of the GEO database (GSE137482) were analyzed.

After analyzing and comparing the 2 group's RNA sequencing data (**Figure 1A**, see Materials and Methods), the genes with high expression with significant fold change in each group were sorted and displayed using volcano plot graphs (**Figure 1B and C**).

I sorted 864 significant genes in 5xFAD mouse brain cortex and 5061 significant genes in MCAO mouse brain cortex with a p value of ≤ 0.05. In addition, there were 401 significant genes with a p value ≤ 0.05 shared between groups.

As depicted in the volcano plot of the 5xFAD model (**Figure 1B**), the expression levels of *Mir6340*, *Abi3bp*, *Tuba1c*, *Cmtm7*, *Gm10801*, *Snord4a*, and *Gm27675* were significantly distinguished in 5xFAD mouse brain cortex compared with those in control brain cortex (**Figure 1B**).

In the volcano plot of the MCAO model (**Figure 1C**), *Epha4*, *Pcna*, *Itgam*, *RP23-49h16.1*, *AF357425*, *Fam64a*, *Nusap1*, *Ccl3*, *Pbk*, *Arg1*, and *Cd3000lf* were significantly distinguished in their expression when comparing MCAO mouse brain cortex with control brain cortex (**Figure 1C**).

To identify commonly altered genes shared by 5xFAD and MCAO mouse groups, genes with a pvalue of ≤ 0.05 in both 5xFAD and MCAO mouse brain cortex were reselected.

In addition, 231 increased genes and 128 decreased genes were identified in both groups (**Supplementary Table 1**). **Figure 2A** shows the 20 most commonly increased genes: *Clec7a*, *Cst7*, *Ccl3*, *Ccl6*, *Ccl4*, *Wfdc17*, *Ifi2712a*, *Bcl2a1b*, *Lyz2*, *Ch25h*, *Milr1*, *Cd52*, *Trem2*, *Lat2*, *Tyrobp*, *Cd48*, *Prkcd*, *Arl11*, *Hcst*, and *Slamf9*. **Figure 2B** shows the 20 most commonly decreased genes: *Gnb1*, *Dnajc27*, *Ttc3*, *Achcyl1*, *Scamps*, *Vamp2*, *Dffa*, *Slc9a6*, *Tspyl1*, *Golga7b*, *Camk2g*, *Cab39*, *Ogt*, *Cstf2t*, *Aco2*, *Plk2*, *Ap3m2*, *Cdkn2aip*, *Tox*, and *Arhgef3*.

To verify related cellular pathways associated with commonly changed genes in the brain cortex of the 5xFAD and MCAO models, the KEGG pathway was analyzed using the MsigDB program (**Figure 3A**). KEGG analysis data for commonly increased genes showed a significant enrichment in the molecular signaling of lysosome, natural killer cell-mediated cytotoxicity, chemokine signaling, antigen processing, cytokine interaction, toll-like receptor signaling, IgA production, and B-cell receptor signaling in the 5xFAD and MCAO groups (**Figure 3A**).

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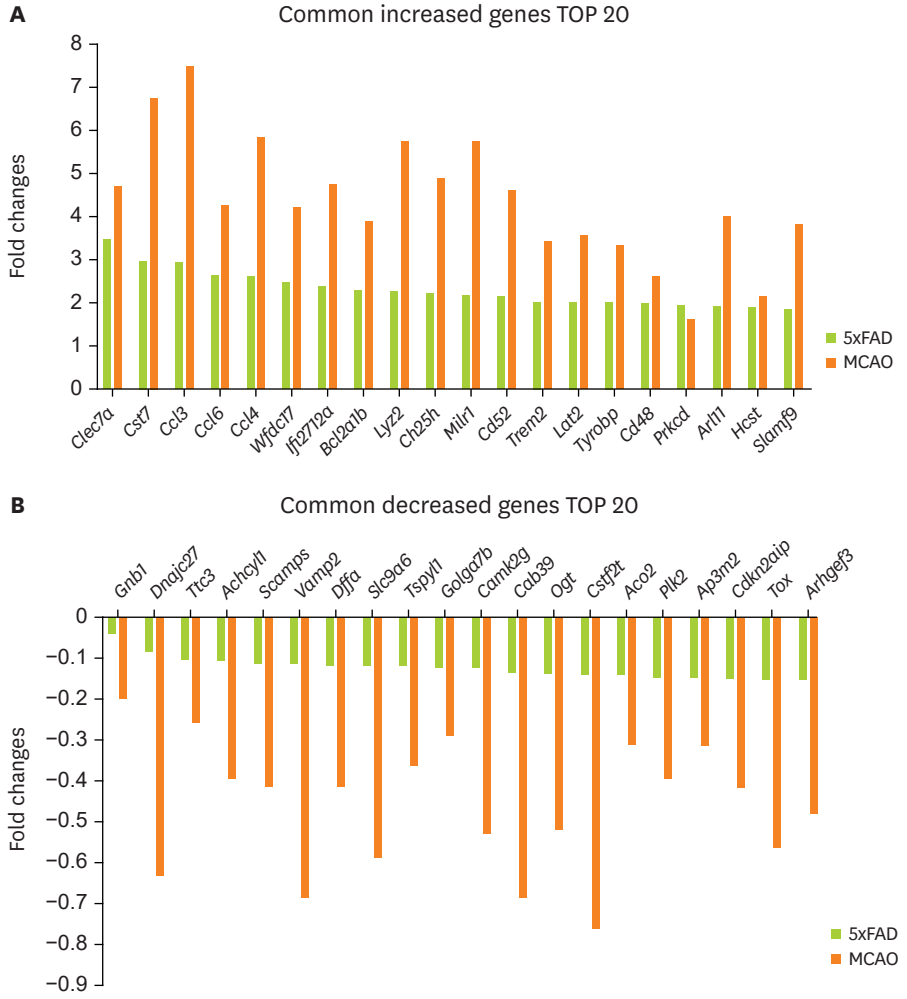

Figure 2. Selected genes with significant expression changes in the mouse brain cortex of MCAO and 5xFAD models. Common genes with a significant expression change in both MCAO and 5xFAD mouse cerebral cortex. Graphs for 20 most commonly (A) increased genes and (B) decreased genes.
MCAO, middle cerebral artery occlusion.

Next, I performed GO analysis for genes commonly increased in both groups (The Gene Ontology Consortium, 2017). The significantly enriched terms included those related to immune response, cell activation, response to biotic stimulus, response to external stimulus, defense response, leukocyte activation, and defense response to other organisms (**Figure 3B**). In addition, I performed a functional clustering analysis of the increased genes using the DAVID functional annotation tool [33] (**Figure 3C**). Highly enriched clusters were linked to synapses, cell junctions, postsynaptic membranes, GTPase activity, cell response of angiotensin, and positive regulation of superoxide anion generation for the commonly changed genes in 5xFAD and MACO mouse brain cortex (**Figure 3C**).

Based on the analyzed data, common characteristics were found between the genes expressed in the cerebral cortex of AD and the genes in the ischemic stroke mouse model.

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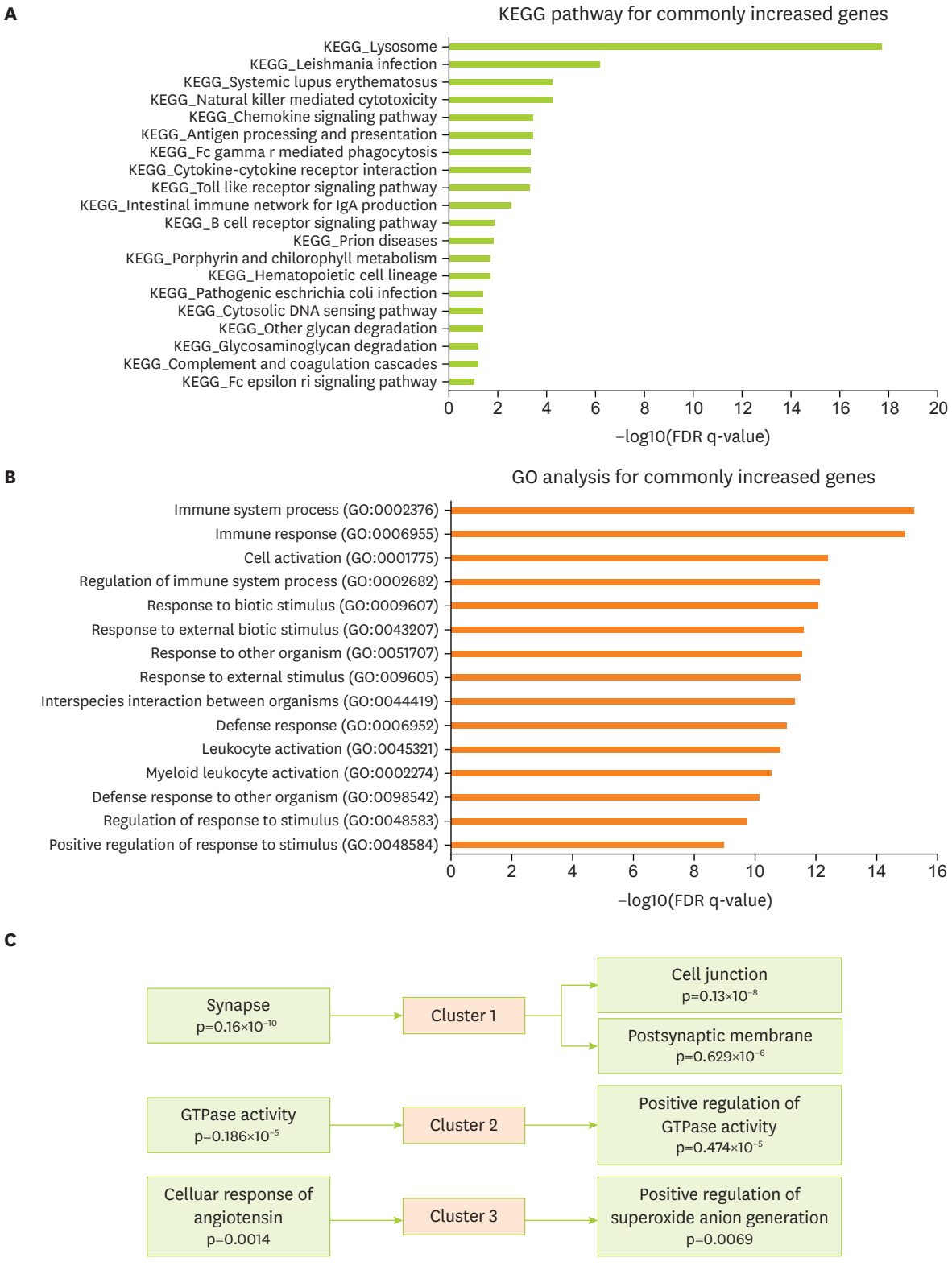

Figure 3. Functional analysis of the commonly increased genes between the MCAO and 5xFAD groups. (A) KEGG pathway analysis of commonly increased genes—significantly altered pathways based on FDR q-value. (B) GO analysis of commonly increased genes. Top 15 GO terms based on FDR q-value. (C) DAVID functional annotation clustering. The top 3 clusters with a significant change are presented.
MCAO, middle cerebral artery occlusion; KEGG, Kyoto Encyclopedia of Genes and Genomes; FDR, false discovery rate; DAVID, Database for Annotation, Visualization and Integrated Discovery; GO, gene ontology.

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DISCUSSION

In this study, I analyzed genes commonly expressed in 5xFAD and MCAO mouse cerebral cortex. Volcano plot shows significant gene expression in 5xFAD and MCAO mouse cerebral cortex. It is found that the expression of the *Tuba1c* gene, which promotes cell proliferation and regulates immune cell infiltration under inflammation conditions [34,35], was significantly distinguished in 5xFAD brain cortex. In addition, the expression of *Cmtm7*, which is associated with immune B-cell antigen receptor regulation [36] and increased risk of obesity [37], was significantly distinguished in 5xFAD brain cortex. These findings suggest that the cerebral cortex in 5xFAD mice may accelerate immune cell infiltration and activate inflammatory responses.

In the MCAO mouse brain cortex, enhanced expression of *Epha4*, which regulates neuronal differentiation and promotes neurogenesis by interacting with platelet-derived growth factor receptor B was identified [38]. Expression of *Nusap1*, which is a microtubule-associated protein related to mitosis and activates glioblastoma [39], was also significantly distinguished in the MCAO mouse brain cortex. In addition, the expression of *Ccl3*, which is a major immune and neurogenesis regulator and plays a role in neuroendocrine function, activates migration of leukocyte, and impairs synaptic plasticity, leading to memory loss [40,41], was significantly distinguished in the MCAO mouse brain cortex.

In the MCAO mouse model, expression of *Cd3000lf*, which leads to microglia activation and severe neuroinflammation [42], was significantly distinguished. Considering these findings, it is thought that the MCAO cerebral cortex had several features such as microglia activation, neuroinflammation, immune cell infiltration, impaired neurogenesis, and synaptic dysfunction.

MCAO cerebral cortex shows alterations shared with AD pathology-related genes (**Figure 2**). The increased expression of *Clec7a* and *Cst7* in the MCAO brain cortex is also routinely found in the microglia of AD brain tissue [43,44]. The increased expression of chemokine *Ccl6* and *Ccl4* observed in the MCAO mouse brain cortex have also been identified in activated microglia and astrocytes in various neurological diseases such as ischemic stroke, AD, and multiple sclerosis [45-47]. Furthermore, increased *Wfdc17* gene expression in MCAO and 5xFAD mouse cerebral cortex implicates immune cell infiltration and immune cell activation [48].

The increased cholesterol 25-hydroxylase expression observed in MCAO mouse brain cortex is also related to impaired cholesterol metabolism in AD [49]. The *Trem2* gene, which is related to microglia activation under amyloid beta toxicity in AD brain [50] was increased in the MCAO and AD mouse brain cortex in this study. Increased *Slamf9* gene expression in the MCAO mouse brain cortex also regulates lymphocytic activation in AD brain [51].

The expression of *Scamps* gene, which controls synaptic plasticity [52], was decreased in MCAO and AD mouse brain cortex. Additionally, the expression of *Vamp2* gene, which is reduced in the hippocampus region and entorhinal cortex and is related to memory formation [53], was reduced in both MCAO and AD mouse brain cortex.

Ogt gene, which regulates postsynaptic plasticity, is reduced in AD brain tissue [54,55]. MCAO and 5xFAD brain cortex showed decreased expression of *Ogt* gene. Decreased *Aco2* gene expression in MCAO brain cortex is related to AD and cognitive decline with mitochondrial dysfunction [56].

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MCAO ischemic stroke brain cortical tissue appears to share characteristics with AD pathology, such as cognitive decline, synaptic dysfunction, lymphocyte activation, glia activation, poor cholesterol metabolism, and inflammation.

KEGG and GO data from this study showed high enrichment of genes related to immune and inflammatory responses, as well as cytokine interaction, in both 5xFAD and MCAO mouse brain cortical tissues. DAVID functional annotation data also suggested a high relationship with inflammatory response, synaptic plasticity, and Rho GTPase, in both 5xFAD and MCAO mouse brain cortical tissues.

Several studies have mentioned that AD brain tissue shows greater activation of immune cells, such as natural killer cells [57,58], and elevated leukocyte infiltration and trafficking [59], leading to memory loss [60]. Synaptic loss is a primary feature of AD [61,62] and is related to postsynaptic density loss in AD brains [63].

Furthermore, the activation of Rho GTPase is observed in AD brains [64] and is related to synaptic stability maintenance and neuronal cell death [65].

Considering previous literature and the findings of this study, I conclude that changes in the cerebral cortex caused by ischemic stroke and AD both result in increased immune response, glia activation, neuronal cell death, inflammation, and Rho GTPase; suppressed synaptic plasticity, neurogenesis, and cholesterol homeostasis; and impaired cognitive function. This suggests that further studies on AD-like cognitive decline after ischemic stroke are necessary for determining the best treatment for memory loss in patients with ischemic stroke.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

The list of common increased and decreased genes in both groups

Click here to view

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