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RESEARCH ARTICLE

A Study of Gene Expression in the Brains of COVID-19, Alzheimer's Disease, and Vascular Dementia Patients

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ABSTRACT: COVID-19 is associated with neurological complications, like the loss of smell, stroke, and dementia. However, it is not well understood how COVID-19 infects brain cells and which processes it affects. The purpose of this study was to investigate the differential and overlapping gene expression in COVID-19, Alzheimer's disease (AD), and Vascular Dementia (VD). Two gene expression datasets were collected from Gene Expression Omnibus. These datasets contained postmortem frontal cortex samples from COVID-19, AD, VD patients, and controls. Then, differential expressed genes (DEGs) were analyzed using GEO2R and Galaxy. Finally, enriched function and pathways were analyzed by DAVID, protein-protein interaction by STRING, and protein-protein docking by HADDOCK. C-C motif chemokine ligand 2 (CCL2), overlapped in three diseases, and was most enriched in the inflammatory pathway. In the docking analysis, the NMR structure of the nonstructural protein 1 (NSP1) from COVID-19 strongly bound to human ribosomal protein S11 (RPS11). These findings suggest that the NSP1 of COVID-19 may directly bind to the brain RPS11, and indirectly cause an inflammatory reaction through CCL2 in the brain.

KEYWORDS: Computational Biology and Bioinformatics; Genomics; COVID-19 neuropathology; Alzheimer's disease; Vascular dementia.

Introduction

COVID-19, a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection,[1] is primarily characterized by respiratory symptoms. The most common symptoms are fever, cough, fatigue, and shortness of breath, but COVID-19 patients also can suffer neurological and psychiatric symptoms.[2,3] COVID-19 neurological symptoms can include seizures, cerebrovascular accidents, encephalopathy, and Guillain-Barré Syndrome.[4] Many of the neurological complications of SARS-CoV-2 infection are related to severe systemic conditions, including multiple organ damage, hypercoagulability, over-activated inflammatory response, and direct infection of the brain.[5]

Multiple studies have found evidence of SARS-CoV-2 in brain samples of COVID-19 infected patients,[6-8] suggesting that SARS-CoV-2 may be responsible for these neurological complications. Indirectly, COVID-19 neuropathology has also been hypothesized to arise as a result of moderate to severe hypoxemia, metabolic dysfunction, systemic inflammation, and immune dysregulation that can contribute to brain dysfunction, all of which have been documented in patients.[9,10] Alzheimer's disease and Vascular dementia, which are common causes of brain degeneration, have been shown to increase the mortality and hospitalization risk for COVID-19 patients.[11] Further, observed activation of microglia in the brains of COVID-19 patients can also be found in patients with neurodegenerative diseases, including Vascular dementia and Alzheimer's disease.[12] These studies suggest that COVID-19 may have unique neuropathology, or an overlapping pathology with other central nervous system diseases.

To date, there has been little research on the effects SARS-CoV-2 on the brain, nor the cellular and molecular mechanisms underlying the neurological changes observed in COVID-19 patients. This study investigated the differential gene expression in postmortem brains of COVID-19 patients and compared them with those of Alzheimer's disease and Vascular dementia patients to identify genes and pathways that may be shared between these three diseases. The common pathways and genes revealed in this study will hopefully provide insight into the neuropathology of COVID-19 and provide candidate targets for future neuro-protective studies in COVID-19 patients.

Methods

Data Sources:

Two datasets that were selected in this study were collected from NCBI's Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/). The first dataset, GSE164332, was created from a study that analyzed post-mortem brain samples of COVID-19, and age and clinical characteristics-matched non-COVID-19 control subjects.[13] Although the post-mortem time of COVID-19 was relatively longer, all the bodies were adequately preserved until the time of the autopsy. The second dataset, GSE122063, was from the study including post-mortem brain samples of Alzheimer's disease, Vascular Dementia and age-matched controls.[14] The GSE164332 dataset investigated the total RNA expression from postmortem brain frontal lobe from nine COVID-19 patients and eight non-COVID-19 controls for comparison, which included patients with Alzheimer's disease and Vascular Dementia. Therefore, only six cases (COVID-19 = 3, non-COVID-19 = 3) without Alzheimer's disease, Vascular Dementia (Table 1) were selected. Microarray analysis was performed using Illumina NextSeq 500 Sequencing, and FastQ files were generated via Illumina bcl2fastq2 (Version 2.17.1.14). Gene expression levels were also quantified and normalized. The GSE122063 dataset analyzed the total

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normalized. The GSE122063 dataset analyzed the total RNA extracted from postmortem brain frontal lobe from individuals who died with Alzheimer's disease (n = 12), Vascular Dementia (primarily of the multi-infarct dementia subtype, n = 9), or without dementia controls (n = 10) (Table 1). Alzheimer's disease was confirmed by no infarct lesions in the autopsied brain hemisphere, and Vascular Dementia was confirmed by no evidence of Alzheimer's disease typical pathological feature. The age, sex, and postmortem interval hours-matched controls were selected. Agilent Human 8x60k v2 microarrays and Bioconductor were used to perform gene expression analysis, and differential expression was carried out using limma.

Table 1: Characteristics of study population from GEO and GSE datasets.

Groups	Age	Sex (M:F)	Postmortem interval (hours)	GEO dataset
COVID-19 (n=3)	79 ± 9.4	1:2	248 ± 98.6	GSE164332
Non-COVID-19 control (n=3)	80.6 ± 2.4	2:1	9.6 ± 5.3	GSE164332
Alzheimer's disease (n=12)	80.9 ± 7.4	4:5	8.0 ± 4.0	GSE122063
Vascular Dementia (n=9)	81.4 ± 10.1	5:7	10.0 ± 4.0	GSE122063
Control (n=10)	78.6 ± 8.5	5:5	9.0 ± 3.0	GSE122063

Differential Gene Analysis:

Galaxy (https://usegalaxy.org/), an online tool that analyzes the gene expression between groups in a GEO dataset, was used to determine the differential expressed genes in GSE164332, and GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r/) in GSE122063. Analyzed results from Galaxy and GEO2R for each dataset were saved to text format files. Genes with a false discovery rate (FDR)-adjusted $p < 0.05$, and a $\log_2$ fold change (FC) cutoff of 1.0 were considered differentially expressed. Genes that met both FDR and logFC cutoffs for each dataset were transported to Excel and used in enriched function analysis. The overlapping genes in the three disease groups were identified using Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/).

Enriched Function Analysis with DAVID and STRING:

The functions and pathway enrichment of candidate DEGs were analyzed using the Database for Annotation, Visualization and Integrated Discovery database (DAVID, https://david.ncifcrf.gov/), which is a web-accessible program that accommodates a comprehensive set of functional annotation tools to investigate the biological roles of genes. The results are presented as dot plots using R Studio and ggplot2 with the enriched functional terms of the molecular function (MF), cellular components (CC), biological process (BP) in Gene ontology (GO) analysis, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. The identified genes from STRING were inputted into DAVID, and $p < 0.05$ was considered as significant. In addition, a count≥2 and EASE >0.1 were considered the cut-off criteria. To analyze the enriched functions that each gene belongs to, the STRING (https://string-db.org/), which predicts direct and indirect protein interactions using online databases and presents a diagram showing important protein–protein interactions (PPI), were used. The differential expressed genes from differential gene analysis were inputted into the STRING, and the minimum interaction threshold was set to the "highest confidence" (>0.9).

Protein-Protein Docking Analysis:

The interactions between SARS-CoV-2 and their target proteins were analyzed to evaluate their binding site and affinity. RPS11 (PDB: 6ZLW) of human 40s ribosome and NSP1 (PDB: 2HSX) of SARS-CoV-2, which was obtained from Protein Data Bank (https://www.rcsb.org/) were selected. These selected proteins were inputted in High Ambiguity Driven protein-protein Docking (HADDOCK, https://wenmr.science.uu.nl/haddock2.4/), a data-driven flexible docking program for the modeling of protein-protein biomolecular complexes. The result of protein-protein Docking was presented by RMSD.

Results

Differential gene expression:

To examine the differentially expressed genes in the postmortem brain of COVID-19 patients as compared to those of non-COVID-19 controls, Galaxy analysis of GSE164332 was performed.[9] 79 over-expressed and 472 down-expressed genes were identified in COVID-19 brain tissue compared to non-COVID-19 controls. The gene *KIAA0319*, which is associated with dyslexia[15] and encodes a protein that plays a role in the developing cerebral cortex by neuronal migration and cell adhesion,[16] was the most over-expressed gene in COVID-19 patients (Table 2). *Myoferlin* (*MYOF*), which encodes a protein that plays a role in membrane regeneration and repair by calcium-mediated membrane fusion,[17] was the most down-expressed gene in COVID-19 patient (Table 3).

Next, GEO2R analysis of GSE122063 was conducted. GSE122063 expression data was derived from a study that compared postmortem frontal lobe samples from Alzheimer's disease or Vascular Dementia patients with samples from controls.[14] This second analysis returned 526 over-expressed and 408 down-expressed genes between Alzheimer's disease patients and control individuals, and 193 over-expressed and 170 down-expressed genes between Vascular Dementia patients and control individuals. In the brains of Alzheimer's disease patients, *corticotropin releasing hormone* (*CRH*) was the most over-expressed gene (Table 2), and *interleukin 1 receptor like 1* (*IL1RL1*), induced by proinflammatory stimuli,[18] was the most down-expressed (Table 3). In the brains of Vascular Dementia patients, *RNA binding motif protein 3* (*RBM3*) gene, induced by low oxygen tension,[19] had the highest expression (Table 2), and *sorting nexin 31* (*SNX31*) gene, involved in protein trafficking,[20] had the lowest expression (Table 3).

Overlapping genes:

In order to determine if there were common gene pathways involved in COVID-19, Alzheimer's disease, and Vascular Dementia patients, genes were screened with conditions of the FDR-adjusted p-value cutoff of 0.05 and logFC cutoff of 1.0 in each dataset, and candidates that overlapped across

Table 2: The top 10 over-expressed genes in postmortem brains of COVID-19, Alzheimer's disease, and Vascular Dementia patients.

COVID-19		Alzheimer dis		Vascular Dementia	
Gene	*logFC*	*Gene*	*logFC*	*Gene*	*logFC*
KIAA0319	3.013166	CRH	2.95	RBM3	2.509663
CDC14C	2.458743	CARTPT	2.81	STMN1	2.150447
ZACN	2.203234	FRMPD2	2.59	CCT6B	2.014873
NPIPA5	2.113072	VGF	2.37	RBM3	1.999349
WASH5P	1.89861	SST	2.32	PBOV1	1.980297
YWHAEP5	1.828757	CTXN3	2.28	LINC00458	1.841953
TP73-AS1	1.806999	GAD2	2.26	PI3	1.744062
DDX18P5	1.754231	PPEF1	2.23	CRH	1.735625
PIM3	1.702827	RBM3	2.13	GUCY2GP	1.720652
PRXL2B	1.680065	PCSK1	2.09	KLHDC7B	1.687498

Table 3: The top 10 down-expressed genes in postmortem brains of COVID-19, Alzheimer's disease and Vascular Dementia patients.

COVID-19		Alzheimer dis		Vascular Dementia	
Gene	*logFC*	*Gene*	*logFC*	*Gene*	*logFC*
MYOF	-5.2812	IL1RL1	-2.7	SNX31	-1.91756
GEMIN5	-5.00056	SERPINA3	-2.48	FCGBP	-1.91508
HDGFL2	-4.95203	SERPINA3	-2.47	SLAMF8	-1.90554
LTA4H	-4.86781	AQP1	-2.29	MIA	-1.88122
GNPAT	-4.45946	SLC1A7	-2.12	CD163	-1.79706
AC104457.2	-4.39108	FCGBP	-2.08	VSIG4	-1.7718
FAN1	-4.36097	CCL2	-2	SIGLEC14	-1.74045
CEP135	-4.32272	SLAMF8	-1.91	SPP1	-1.68427
SERPINI2	-4.27884	HMBOX1	-1.9	RNASE2	-1.61027
KMO	-4.25159	CHRM4	-1.88	AQP1	-1.6017

COVID-19, Alzheimer's disease, and Vascular Dementia were collected. This analysis revealed 67 differentially over-expressed genes and 105 differentially down-expressed genes that overlap in COVID-19, Alzheimer's disease, and/or Vascular Dementia patients (Figure 1). In particular, three over-expressed genes in Alzheimer's disease samples that overlapped with COVID-19 that were of interest included *neuronal pentraxin 2* (*NPTX2*), growth-regulating estrogen receptor binding 1 (*GREB1*) and *allograft inflammatory factor 1-like* (*AIF1L*) (Figure 1A). Additionally, for COVID-19 and Alzheimer's disease, five down-expressed overlapping genes were found: *posphatidate phosphatase LPIN30* (*LPIN3*), *serglycin* (*SRGN*), *solute carrier family 7 member 2* (*SLC7A2*), *caspase recruitment domain family member 6* (*CARD6*), and *Ral guanine nucleotide dissociation stimulator like 4* (*RGL4*) (Figure 1B). In all three diseases, *ribonuclease A family member 2* (*RNASE2*) and *C-C motif chemokine ligand 2* (*CCL2*) were identified (Figure 1B). These results suggest that inflammation-related genes are involved in the pathology of COVID-19, Alzheimer's disease, and Vascular dementia.

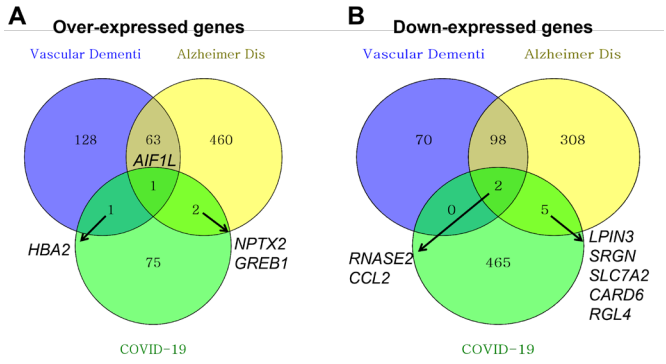

Figure 1: Number of overlapping genes of (A) over-expressed genes and (B) down-expressed genes in brain samples from COVID-19 (green), Alzheimer's disease (yellow), and Vascular Dementia (blue) patients.

Statistical Evaluation:

To analyze the enriched functions and pathways that differential expressed and overlapping genes belong to, 551 differentially expressed genes of COVID-19, 934 genes of Alzheimer's disease, 363 genes of Vascular Dementia, and 182 overlapping genes of the three diseases were analyzed using enriched gene ontology (GO) analysis. The enriched functions and pathways of the candidate differentially expressed genes were evaluated using the DAVID bioinformatics website.

Analysis revealed differentially expressed genes (DEGs) of COVID-19 samples were enriched in viral transcription, viral gene expression, and co-translational protein targeting to membrane pathways in the BP ontology (Figure 2A). In the CC ontology, aberrantly expressed genes were enriched in the ribosomal subunit and cytosolic ribosome. In the MF ontology, structural constituents of ribosomes were the main areas of enrichment. According to the KEGG pathway enrichment analysis, DEGs were enriched in transcriptional misregulation and the ribosome signaling pathway in COVID-19 samples (Figure 2A). These data indicate that the coronavirus infection is associated with changes in gene expression and specifically the ribosomal pathway.

In the Alzheimer's disease samples, the pathways of signaling, cell communication, nervous system development, and synaptic signaling were enriched in the BP ontology while the pathways involved in synapse and neuron projection were enriched in the CC ontology (Figure 2B). In addition, neurotransmitter receptor activity was enriched in the MF ontology (Figure 2B). Lastly, the pathways involved in neuroactive ligand-receptor interactions as well as inhibitory GABAergic synapses were enriched in KEGG pathway (Figure 2B). These data indicate that genes involved in excitatory and inhibitory synaptic neurotransmission are upregulated in the brains of Alzheimer's patients. In Vascular Dementia, G protein-coupled receptor signaling pathways were enriched in the BP ontology, and Neuroactive ligand-receptor interaction were enriched in KEGG pathway (Figure 2C).

The overlapping pathways enriched in COVID-19, Alzheimer's disease, and Vascular Dementia included chemotaxis, immune response, inflammatory response, positive regulation of immune complex clearance by monocytes and macrophages, regulation of isotype switching, regulation of vascular endothelial growth factor production, type 2 immune response, and positive regulation of the major histocompatibility complex (MHC) class II biosynthetic process in the BP ontology (Figure 2D). Gene products within the extracellular region and extracellular space were enriched in the CC ontology, while CCR2 chemokine receptor binding and ribonuclease activity were enriched in the MF ontology, and cytokine-cytokine receptor interaction were enriched in KEGG pathway (Figure 2D). These data indicate that inflammation, particularly related with monocyte/macrophages and CCR2, is a common pathological feature in these three diseases.

Protein-Protein Interaction:

To construct a protein-protein interaction (PPI) network of differential expressed and overlapping genes, the enriched PPI were analyzed. 551 differentially expressed genes of

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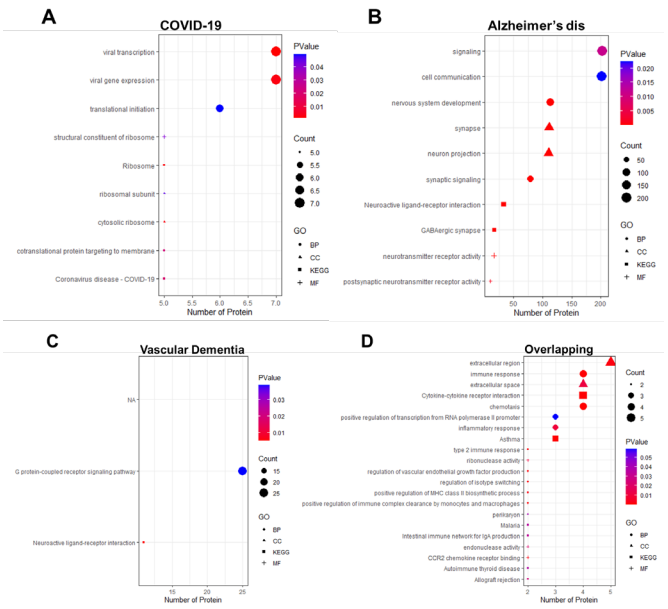

Figure 2: Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway of (A) COVID-19, (B) Alzheimer's disease, (C) Vascular dementia, and (D) the overlapping genes enriched in these three diseases.

COVID-19, 934 genes of Alzheimer's disease, 363 genes of Vascular Dementia, and 182 common genes of three diseases were inputted into the STRING to find PPI. PPI analysis revealed that *ribosomal protein S11* (*RPS11*) of COVID-19, *brain-derived neurotrophic factor* (*BDNF*) of Alzheimer's disease, *G protein subunit gamma 13* (*GNG13*) of Vascular Dementia, and *C-C motif chemokine ligand 2* (*CCL2*) were identified as highest-ranked interacting hub genes (Figure 3).

The *RPS11* hub gene in COVID-19 samples was chiefly enriched in the ribosome pathway, and *BDNF* in Alzheimer's disease samples was chiefly enriched in the GABAergic synapse pathway, while *GNG13* in Vascular Dementia was chiefly enriched in G protein-coupled receptor signaling pathway (Figure 3A-3C). The common hub gene of these three diseases, *CCL2*, was chiefly enriched in cytokine-cytokine receptor interaction (Figure 3D).

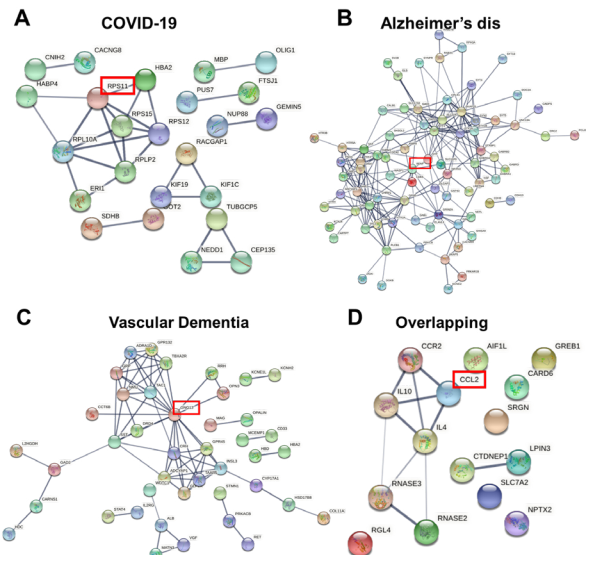

Figure 3: Protein-Protein Interactions of (A) COVID-19, (B) Alzheimer's disease, (C) Vascular dementia, and (D) overlapping genes of these three diseases.

Protein-Protein docking:

To evaluate whether the RPS11 hub protein from enriched functional analysis could interact with the SARS CoV-2 protein, molecular docking tools were employed to analyze the interaction of the Nonstructural protein 1 (NSP1) from the SARS coronavirus (PDB: 2HSX) with human RPS11 (PDB: 6ZLW). In this study, the SARS-CoV N-terminal NSP1 was selected because it is a major virulence factor of SARS-CoV-2.[21] Protein-protein interaction complexes were analyzed using the HADDOCK 2.4 server which is a computational tool that allows the simulation of protein-protein molecular interaction. As a result, the HADDOCK energy score of this interaction was -75.9 ± 1.7, overall RMSD was 0.5 ± 0.4Å, Van der Waals energy was -23.9 ± 1.7, and the Z-score was -1.7 (Figure 4).

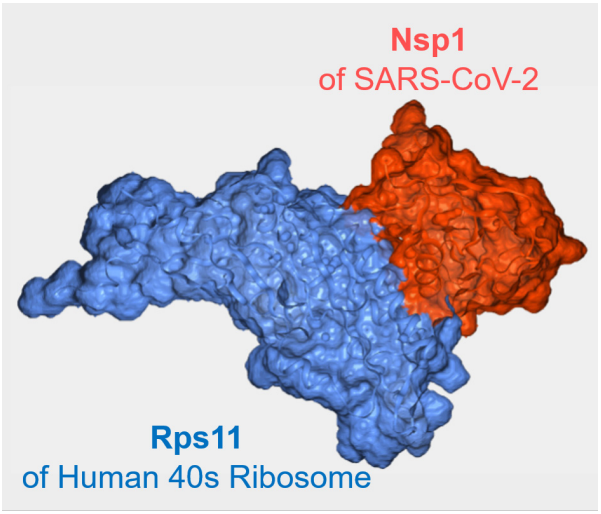

Figure 4: Protein-Protein docking of NMR Structure of the nonstructural protein 1 (NSP1) from the SARS coronavirus (PDB: 2HSX) and human ribosomal protein S11 (RPS11) (PDB: 6ZLW).

■ Discussion

The data presented here shows that in the brains of COVID-19, Alzheimer's disease, and Vascular dementia patients the genes *RPS11* of COVID-19, *BDNF of Alzheimer's disease*, *GNG13* of Vascular Dementia, and *CCL2* of all three diseases are interacting hub genes when compared to control individuals. To hypothesize the role of these genes in a disease context requires some background into what is known about these genes.

RPS11, enriched in COVID-19 samples, encodes a ribosomal protein S11 located in the cytoplasm.[22] Here, it can be seen that there is a strong interaction between the RPS11 protein and the SARS CoV-2 protein using molecular docking tools. Indeed, another group has reported that NSP1, a major virulence factor of SARS-CoV-2, binds to the 40s ribosomal subunit of RPS11 and suppresses host gene expression.[21] Given that other studies have also detected SARS-CoV-2 in brain tissue,[6, 7, 23] this presents an intriguing potential mechanism for COVID-19 neuropathology. Specifically, if NSP1 of SARS-CoV-2 could invade the human brain and bind to 40s

ribosomal subunit of RPS11, this could result in impaired ribosome function, and consequently, decreased protein synthesis in neurons leading to neurodegeneration, and potentially the brain fog that is experienced by patients.

Here it was found that *BDNF* is enriched in the GABAergic synapses in Alzheimer's disease brain samples. The *BDNF* gene encodes a protein which modulates control of growth, differentiation, and maintenance of neurons in the brain and spinal cord.[24] BDNF regulates the synaptic plasticity between nerve cells, playing an important role in learning and memory.[25] In Alzheimer's disease, amyloid-beta is thought to target GABA interneurons[26] which may result in indirect activation of BDNF[27] and a shift in the balance of excitatory/inhibitory activity in the brains of patients. In this study, *GNG13* was found to be chiefly enriched in the G protein-coupled receptor signaling pathway in Vascular Dementia samples. *GNG13* encodes the guanine nucleotide-binding protein subunit gamma-13. G proteins, like GNG13, are signal transducing molecules in the cytoplasm. G proteins can function as monomeric small GTPases or form heterotrimeric G protein complexes (GPCRs) to function as membrane bound GTPases. G proteins and GPCRs transfer the signals from hormones, neurotransmitters, and chemokines, as well as modulate enzymes, neurochemistry, and transcriptional factors.[28] The disruption of GPCRs are implicated in many diseases, including diabetes, allergies, depression, cardiovascular diseases,[29] and neurodegenerative diseases such as Vascular Dementia.[30] Vascular Dementia is caused by restricted blood flow to the brain, which can be caused by impairment of the cerebral blood vessel system, resulting in neuron death.[31] GPCRs play important roles in various pathophysiological disorders including circulatory diseases[28] and not surprisingly, are commonly targeted for medicinal therapeutics.

Interestingly, the CCL2 inflammatory gene and inflammatory response pathway were enriched in COVID-19, Alzheimer's disease, and Vascular dementia. CCL2, or Monocyte chemoattractant protein 1 (MCP1), is a chemokine which recruits inflammatory monocytes to the inflammation site induced by tissue injury or infection.[32] There is increasing evidence showing overlap of cerebrovascular and neurodegenerative pathology in Alzheimer's disease and Vascular Dementia.[33] In Alzheimer's disease, CCL2 is increased both in brain tissue and in cerebrospinal fluid (CSF), and overexpression of CCL2 is associated with amyloid deposition.[34] In the ischemic state of Vascular Dementia, CCL2 disrupts blood-brain barrier (BBB) permeability, recruits inflammatory monocytes to the brain, where they pass through BBB and are differentiated into microglia producing neurotoxic and inflammatory molecules.[35, 36] The systemic cytokine analysis of severe COVID-19 showed the significantly higher level of CCL2.[37] Furthermore, an elevated levels of CCL2 in the CSF of COVID-19 patients were reported.[38]

SARS-CoV-2 in the brain results in a markable increase of microglia and astrocyte subpopulations and broad over-expression of inflammatory genes in the choroid plexus cells of COVID-19 patients.[11] This microglia phenotype shares features with neurodegenerative diseases that have previously been reported. These results, in combination with the findings of this study, suggest that SARS-CoV-2 infection could directly affect the brain, cause inflammation, and possibly cause a patient's neurological symptoms.

Conclusion

Taken together, this research has provided evidence linking important pathways that may function in the pathology of COVID-19, Alzheimer's disease, and Vascular dementia. From this data, it is hypothesized that, NSP1 of SARS-CoV-2 binds to RPS of 40s ribosome in neurons, suppressing gene expression, and contributing to CCL2 inflammatory reaction in the cerebral cortex, resulting in neuronal degeneration. To confirm this hypothesis, further studies will need to be conducted to support these links, but the data gathered here will hopefully be utilized for future studies into therapeutics for the preservation of brain function in COVID-19 patients.

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