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Genetic Exchange of Lung-Derived Exosome to Brain Causing Neuronal Changes on COVID-19 Infection

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Abstract

The pandemic of novel coronavirus 2 (SARS-CoV-2) has made global chaos for normal human living. Despite common COVID-19 symptoms, variability in clinical phenotypes was reported worldwide. Reports on SARS-CoV-2 suggest causing neurological manifestation. In addition, the susceptibility of SARS-CoV-2 in patients with neurodegenerative diseases and its complexity are largely unclear. Here, we aimed to demonstrate the possible transport of exosome from SARS-CoV-2–infected lungs to the brain regions associated with neurodegenerative diseases using multiple transcriptome datasets of SARS-CoV-2–infected lungs, RNA profiles from lung exosome, and gene expression profiles of the human brain. Upon transport, the transcription factors localized in the exosome regulate genes at lateral substantia nigra, medial substantia nigra, and superior frontal gyrus regions of Parkinson's disease (PD) and frontal cortex, hippocampus, and temporal cortex of Alzheimer's disease (AD). On SARS-CoV-2 infection, BCL3, JUND, MXD1, IRF2, IRF9, and STAT1 transcription factors in the exosomes influence the neuronal gene regulatory network and accelerate neurodegeneration. STAT1 transcription factor regulates 64 PD genes at lateral substantia nigra, 65 at superior frontal gyrus, and 19 at medial substantia nigra. Similarly, in AD, STAT1 regulates 74 AD genes at the temporal cortex, 40 genes at the hippocampus, and 16 genes at the frontal cortex. We further demonstrate that dysregulated neuronal genes showed involvement in immune response, signal transduction, apoptosis, and stress response process. In conclusion, SARS-CoV-2 may dysregulate neuronal gene regulatory network through exosomes that attenuate disease severity of neurodegeneration.

Keywords SARS-CoV-2 · Covid-19 · Exosome · Neurodegeneration · Parkinson's disease · Alzheimer's disease

Introduction

Exosomes are one of the extracellular vesicles secreted by most of the multi-cellular organisms for their intercellular communication. Exosomes carry various biomolecules like nucleotide molecules, including RNA, miRNAs, lncRNA, proteins, and metabolites from the originating cells to target cells [1, 2]. Initially, exosomes were considered to be involved in removing waste molecules from the cells [3]. Advance in the research suggests that exosomes deliver micro- and macromolecules to communicate and regulate the recipient cells during physiological and pathological processes. It is proven that exosomes are involved in cancer progression [4], cardiovascular diseases [5], neurodegeneration [6], and even in microbial and viral infections [7, 8]. Interestingly, exosomes released from the virus-infected cells carry the viral particles to reprogram the target cells and spread pathogenesis [9].

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Recently, the SARS-CoV-2 (COVID-19) infection has become a pandemic affecting millions of people worldwide. An increased vulnerability is reported in patients with chronic diseases like diabetes and hypertension [10, 11]. SARS-CoV-2 infects lower respiratory tracts and progresses toward multi-organ failure [12]. Currently, there is no specific treatment available to treat COVID-19. Social distancing and vaccination are helpful to protect the spreading of disease among the population. However, there is an urgent need to develop a drug to treat this disease. Understanding the disease mechanism may contribute to the development of a potential drug for SARS-CoV-2 infection. Many viruses, including the RNA of SARS-CoV-2, are known to enter the exosome that enables intra-host spreading [13]. Studies showed presence of SARS-CoV-2 viral particles within exosomes [14, 15]. Besides, SARS-CoV-2 was noticed within host cells' vacuoles in the histopathological analysis [16, 17]. These findings suggested a possible involvement of exosomal intercellular communication on SARS-CoV-2 infection from the primary lung site to other communicating organs in the human system.

Among various affected organs, limited research has been carried out to study the COVID-19 pathogenesis in the brain. Besides the cardinal symptoms, neurological changes have also been reported in 36.4% of cases COVID-19 [18]. Notably, some COVID-19 recovered patients show significant memory loss and cognitive disability [19]. Recently, Singh et al. suggested that COVID-19 may affect the central nervous system (CNS) [20]. Particularly, a few studies suggest COVID-19 may accelerate neurodegeneration in Parkinson's (PD) and Alzheimer's (AD) disease [21, 22]. A study by Pavel et al. suggests COVID-19 causes selective vulnerability in PD by activation of α-synucleinopathies in the CNS [21]. Also, the survey conducted by Brown et al. reports the worsening of PD symptoms on COVID-19 infection [23]. Similarly, Naughton et al. demonstrate the possible role of COVID-19 infection in patients with AD [24]. Moreover, Heneka et al. suggest that COVID-19 patients are at high risk of developing AD [25].

Herein, we postulate that exosomes may be involved in the transport molecules from the infected lungs to the brain region by crossing the blood–brain barrier (BBB) that leads to neurological manifestation. Elevated levels of exosomes in the peripheral circulatory system were noticed during lung inflammation [26]. Indeed, previous studies have demonstrated the exosomal transport between the lungs to BBB and BBB to other neuronal regions [27–32]. In general, BBB is a vascular structure composed of brain microvascular endothelial cells (BMECs), which act as a barrier between the CNS and peripheral circulatory system that allows exosomes in and out from blood to the brain. Studies suggest exosomal transport occurs by endocytosis of BMEC's transcellular mechanism or diffusion through tight junctions between BMECs [33, 34]. Recently, Reynolds et al. suggest the ability of SARS-COV-2 to alter tight junction (TJ) proteins that cause disruption of BBB integrity which allows neuro-invasion of molecules [35]. Chen et al. demonstrate exosomes crossing BBB through transcellular BMEC endocytosis in stroke [36]. Similarly, Matsumoto et al. report the transport of exosomes from the peripheral circulatory to CNS through BBB during the inflammatory condition [37].

In the present study, we have developed a systems biological framework to demonstrate the role of exosome-carried mRNAs that encode transcription factors from infected lungs to the brain. We investigated multiple transcriptome datasets of SARS-CoV-2–infected lungs, RNA profiles of lung-derived exosomes, and gene expression profiles of various human brain regions. In addition, the exosomal intercellular network between lungs and brain regions was constructed for neurodegenerative diseases based on literature evidence. Our data identify the transcription factors (TF) from the lungs regulating gene expression in the brain regions, which accelerate PD and AD on COVID-19 infection.

Materials and Methods

Data Collection

The RNA-Seq dataset related to SARS-CoV-2 infection in the lungs were retrieved from Sequence Read Archive (SRA), NCBI database by using a combination of key terms including "SARS-CoV-2" and "Human host." The dataset (GSE147507) containing the RNA-Seq profile of 110 samples at various experimental conditions of SARS-CoV-2 infection was retrieved [38]. Among 110 samples, two healthy lung biopsies (GSM4462413 and GSM4462414) and two SARS-CoV-2–infected lung (GSM4462415 and GSM4462416) samples were selected and utilized for our downstream analysis. These selected samples have no previous history of disease including neuropathology.

RNA-Seq Expression Analysis

FastQC v0.11.5 was used to assess the quality of data. Then, reads were trimmed by using Trimmomatic v0.32. The qualified reads were aligned to the HG19 human genome. Reads count for each transcript was normalized, and the up-regulated genes on SARS-CoV-2 infection compared to healthy lungs were captured using the DESeq method. Significant up-regulated genes were identified based on false discovery rate (FDR), $p < 0.05$.

Lung Exosome Profile

The GSE121307 microarray dataset [39] describing the exosomal shuttle RNA (esRNA) in respiratory tract–derived exosomes was collected from NCBI, Gene Expression Omnibus (GEO) database. Exosomal shuttle mRNA (esRNA) predominantly expressed in GSE121307 lung data were identified and mapped with the overexpressed genes on SARS-CoV-2 infection. The mapped overexpressed genes were assumed to be packed into exosome as esRNA during SARS-CoV-2 infection. Among them, mRNA encoding transcription factor was identified using the Molecular Signatures (https://www.gsea-msigdb.org/gsea/msigdb) and TcoF-DB (https://tools.sschmeier.com/tcof) databases.

Exosome Communication Network from Literature Data

The Qinsight text mining tool (https://quertle.com/) was used to construct an exosome–cell communication network. Qinsight allows us to collect more precise literature for the key terms from patents, clinical trials, and journals, including original research, reviews, and case reports based on biospecific artificial intelligence methods. We constructed the exosome communication network by literature search with the relevant keywords to establish the exosome connection between (1) lungs to the BBB and (2) BBB to the neuronal regions associated to PD and AD. At the initial phase of exosome communication network construction, anatomical neuronal connectivity between the brain regions and BBB was verified. In the second phase, the report suggesting the transport of exosomes between the lungs and the BBB and subsequent transfer of exosomes from the BBB to neuronal regions was accessed. In both phases, two different investigators (M.K. and P.P.) independently collected the supporting literature using Qinsight. The collected data were cross-verified by the two investigators (S.S.S.J.A. and A.S.). If any, discrepancy in the collected data was resolved during group discussion. Finally, based on the literature evidence, an exosome communication network was constructed.

Neurodegenerative Disease Expression Profile

The Parkinson's gene expression microarray dataset of human lateral substantia nigra, medial substantia nigra, and superior frontal gyrus regions was retrieved from the Gene Expression Omnibus (GSE8397) [40]. For AD, the gene expression dataset of human frontal cortex, hippocampus, and temporal cortex was collected with accession GSE36980 [41]. The sample characteristics of both datasets (GSE8397 and GSE36980) were assessed from the literature [40, 41]. In the PD dataset (GSE8397), all control samples were reported free from neurological diseases and PD cases were assessed by neurological rating scale and histologically confirmed [40]. Particularly, the multiple sclerosis–specific control sample in the GSE8397 dataset was excluded during analysis. Similarly in the AD dataset (GSE36980), Binswanger's disease and non-AD vascular dementia were excluded to select control samples that are free from neurological diseases [41], whereas the AD samples were pathologically assessed based on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) and the Braak stage positive. In addition, the AD was confirmed with immunostaining against phosphorylated microtubule-associated protein tau [41]. All selected samples from the datasets were log-transformed and analyzed with a limma 3.26.8 library package using the R program to identify significantly overexpressed genes (DEG) with a *t* test statistical significance of $p \leq 0.05$.

TF Regulating Genes

Next, we assumed that exosome-transported mRNA encoding TF would be readily translated into protein by the host translational machinery and activate its target genes in neurons. These activated genes may be associated with neurodegenerative diseases. We use the Coexpedia database (http://www.coexpedia.org/) to look for overexpressed PD and AD genes that are co-expressed with each TF identified in the exosomes during SARS-CoV-2 infection. The regulatory relationships were determined between these TFs with overexpressed PD and AD genes using iRegulon plugin (version 1.3) in Cytoscape software [42] with NEScore > 3 and FDR < 0.001 set as a threshold [43].

Molecular Enrichment

Molecular enrichments were carried out to evaluate the TF's target genes' functions and relevance for the PD and AD pathology. The biological process of the genes in the regulatory network was determined by using the BiNGO module [44] with a *p* value < 0.05 cut-off in Cytoscape software. The regulatory network was also analyzed based on molecular pathways derived using the Reactome database (www.reactome.org/).

Results

RNA-Seq Analysis and esRNA

Lung RNA-Seq data on SARS-CoV-2 infection and their controls were analyzed. Of 21,797 transcripts, 731 (431 up and 300 down) were differentially regulated on SARS-CoV-2 infection with FDR, $p < 0.05$. We then mapped the 431 overexpressed genes with GSE121307 esRNA data to confirm their lung-derived exosome. We believe that the flooding of

overexpressed genes in the lungs in SARS-CoV-2 infection may be packed into exosomes and transported to the target cell. Among 431 overexpressed genes, 267 were sorted into exosomes. For example, GSK3B, DPP4, SMAD3, PARP1, and IKBKB are the inflammatory genes (mRNA) noticed as an outcome of cytokine storm in the lungs that may be carried as esRNA to target cells by the exosome. Of 267 overexpressed esRNA, 19 encode TFs identified using the Molecular Signatures and TcoF-DB v2 databases (Table 1).

Exosomal Communication Network

Next, we constructed an exosomal communication network based on literature evidence. The network demonstrates the exosomal connectivity between the lungs and BBB microendothelial cells [27–32]. Similarly, the exosome communication between the BBB endothelial cells and various neuronal regions was determined based on literature evidence [27–32]. Overall, the exosomal network confirms the exosomal connectivity between lungs and neuronal regions associated with neurodegenerative diseases through BBB (Fig. 1).

Over-representation of Genes in Neurological Diseases

Simultaneously, the collected microarray datasets of PD at lateral substantia nigra, medial substantia nigra, and superior frontal gyrus region were analyzed to identify the overexpressed genes at each neuronal region compared to its control. The overexpressed genes with a p value ≤ 0.05 were selected at each condition across the neuronal regions. For instance, 2495 genes at the lateral substantia nigra, 1088 at the medial substantia nigra, and 790 at the superior frontal gyrus region of PD were overexpressed compared to control. Similarly, the analysis of AD datasets showed 362 genes at the frontal cortex, 1935 in the hippocampus, and 1242 at the temporal cortex were noticed overexpressed in AD.

TF–Gene Regulatory Network

Transcription factor is a regulatory component involved in regulating cellular gene expression. Here, we built a TF–gene network for 19 TFs regulating the overexpressed PD and AD genes across the brain regions. The acquired TFs from the exosomes will be readily translated into protein by the neuronal translational machinery of targeted neurons. After that, the TFs initiate the transcription of their target genes on binding to their promoter region. We noticed 2758 genes were co-expressed along with the selected 19 TFs (Fig. 2). Using iRegulon, the six transcription factors showed regulating the overexpressed genes in neurodegenerative diseases at lateral substantia nigra (Fig. 3), medial substantia nigra (Fig. 4), superior frontal gyrus (Fig. 5), frontal cortex (Fig. 6), hippocampus (Fig. 7), and temporal cortex (Fig. 8). For instance, STAT1 regulates 64 genes associated with PD at lateral substantia nigra. In medial

Table 1 Transcription factors localized into lung-derived exosome on COVID infection

Transcription factor	Description	Chromosome location
BCL3	B-cell CLL/lymphoma 3	19q13.1–q13.2
BLOC1S1	Biogenesis of lysosomal organelles complex-1, subunit 1	12q13–q14
HESX1	HESX homeobox 1	3p14.3
IRF2	Interferon regulatory factor 2	4q34.1–q35.1
IRF9	Interferon regulatory factor 9	14q11.2
JUND	Jun D proto-oncogene	19p13.2
LITAF	Lipopolysaccharide-induced TNF factor	16p13.13
MIER1	Mesoderm induction early response 1, transcriptional regulator	1p31.3
MXD1	MAX dimerization protein 1	2p13–p12
NFKBID	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, delta	19q13.12
PHF11	PHD finger protein 11	13q14.2
SP110	SP110 nuclear body protein	2q37.1
SP140	SP140 nuclear body protein	2q37.1
SP140L	SP140 nuclear body protein-like	2q37.1
STAT1	Signal transducer and activator of transcription 1, 91 kDa	2q32.2
STAT4	Signal transducer and activator of transcription 4	2q32.2–q32.3
TRIM22	Tripartite motif containing 22	11p15
TRIM38	Tripartite motif containing 38	6p21.3
ZNF385A	Zinc finger protein 385A	12q13.13

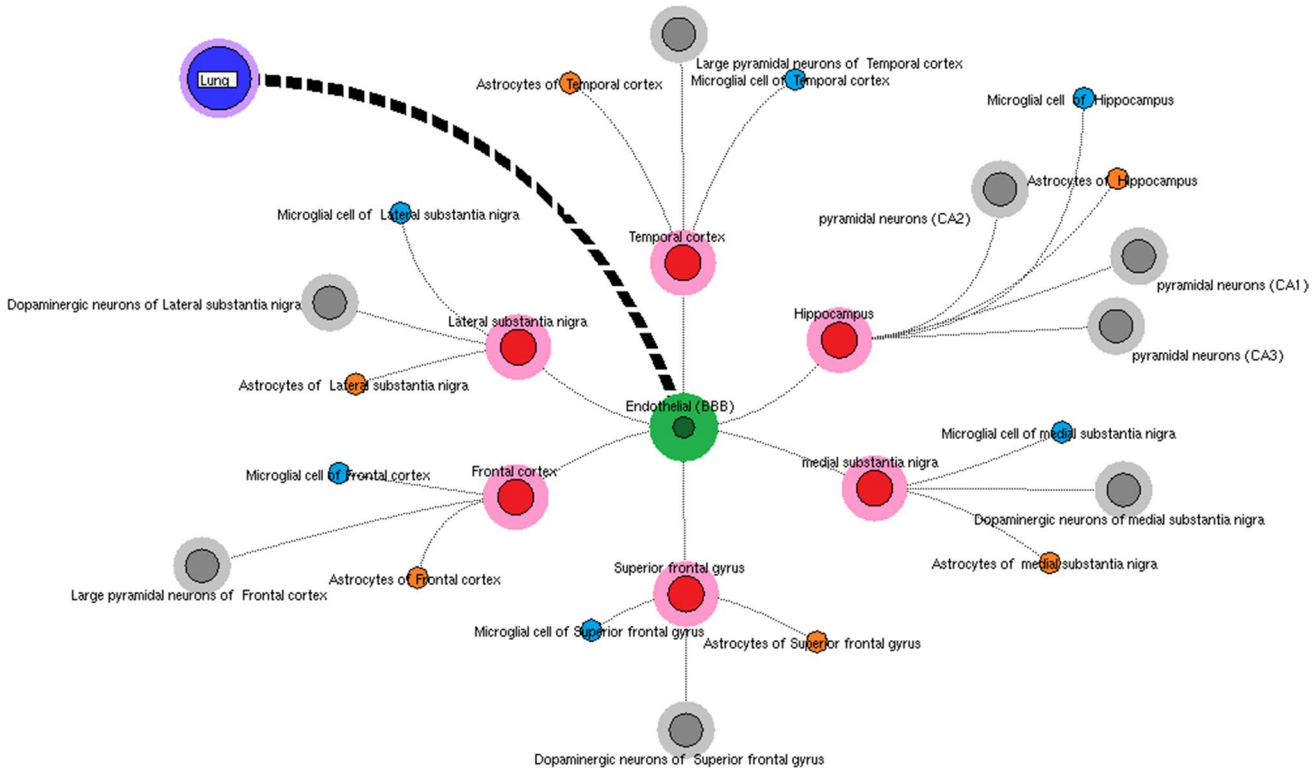

Fig. 1 Exosomal communication network. Network representing the exosomal connectivity between lungs to the neuronal regions associated with neurodegenerative diseases through the blood–brain barrier (BBB). The lungs are represented as violet node defining connection with the BBB (green node) by bold dotted edges. BBB connects various brain regions associated with PD (yellow) and AD (red). The gray-colored nodes represent the neurons, orange nodes represent astrocyte, and blue nodes represent microglia cells

substantia nigra, STAT1 regulates 19 PD genes, whereas at superior frontal gyrus region, STAT1 regulates 65 genes related to PD. Similarly, in AD, STAT1 regulates 74 AD genes at the temporal cortex. STAT1 regulates 40 genes in the hippocampus, whereas at frontal cortex regions, STAT1 regulates 16 genes related to AD.

Molecular Enrichment

We investigated the biological process of each regulatory network in PD (Supplementary Material 1) and AD (Supplementary Material 2), which showed dysregulation in the immune response, signal transduction, apoptosis, and response to stress metabolism. Furthermore, the pathway analysis of the PD regulatory network showed regulating TRAIL signaling pathway, estrogen receptor signaling, Alpha9 beta1 integrin signaling events, LKB1 signaling events, ErbB receptor signaling network, Sphingosine 1-phosphate (S1P) pathway, mTOR signaling pathway, internalization of ErbB1, S1P1 pathway, Arf6 trafficking events, and insulin pathway (Fig. 9). Similarly, the AD regulatory networks significantly enriched and contributed to the TRAIL signaling pathway, IL5-mediated signaling events, Syndecan-1 signaling, estrogen receptor signaling, proteoglycan, focal adhesion kinase signaling, urokinase-type plasminogen activator (uPA), and uPAR-mediated signaling (Fig. 10).

Discussion

The mechanism of COVID-19 causing neurological manifestation is not clearly understood. The current study suggests that COVID-19 accelerates the immune process and oxidative stress causing difficulty in patients with neurodegenerative diseases [45]. The complexity of the neurodegenerative process and the significant involvement of newly emerged pandemic COVID-19 make it necessary to investigate the association of COVID-19 in PD and AD, the most prevalent neurodegenerative diseases worldwide.

In the present study, the complex systems biological framework was implemented that integrates various transcriptome datasets to demonstrate the influence of exosomal transporting molecules from the lung to the brain on COVID-19 infection. During inflammation, lung cells release exosomes that carry the abundance of signaling molecules to avoid cellular stress. We identified 19 transcription factors (LITAF, IRF2, IRF9, PHF11, ZNF385A, MIER1,

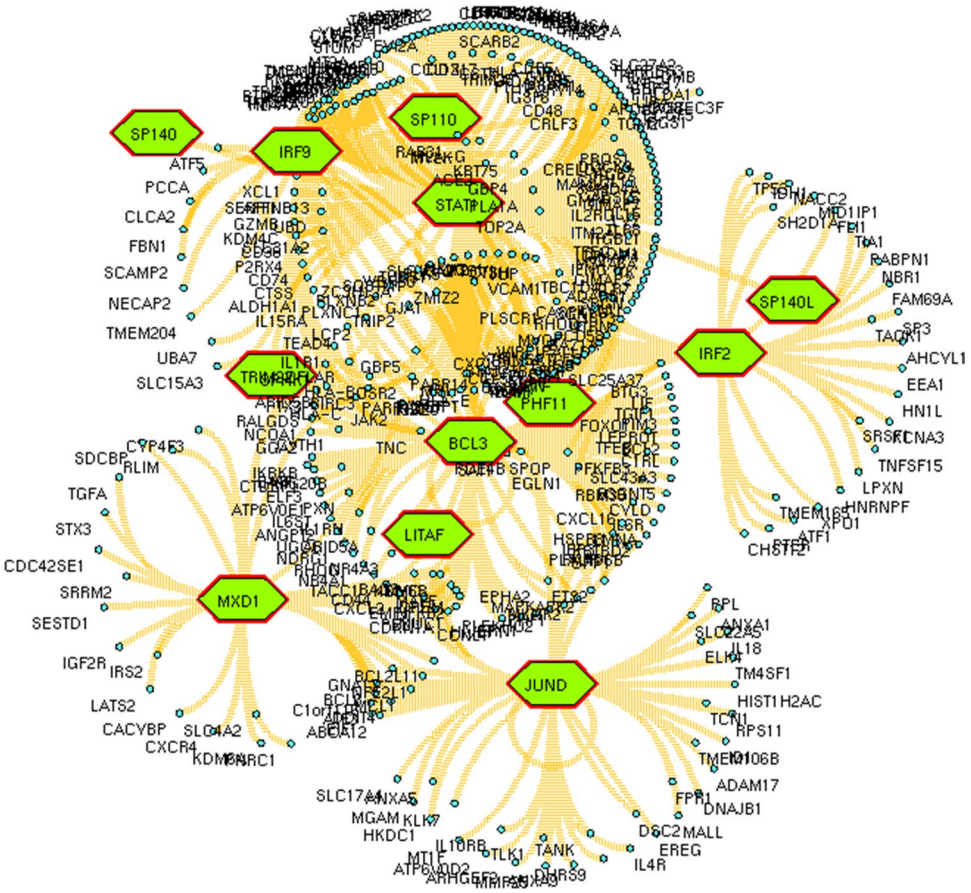

Fig. 2 Co-expressed network of neurodegenerative disease genes with TFs. Network representing the co-expressed up-regulated genes (blue ellipse) in PD and AD along with the 19 transcription factors (green polygon) transported from the lung through exosome on COVID-19 infection

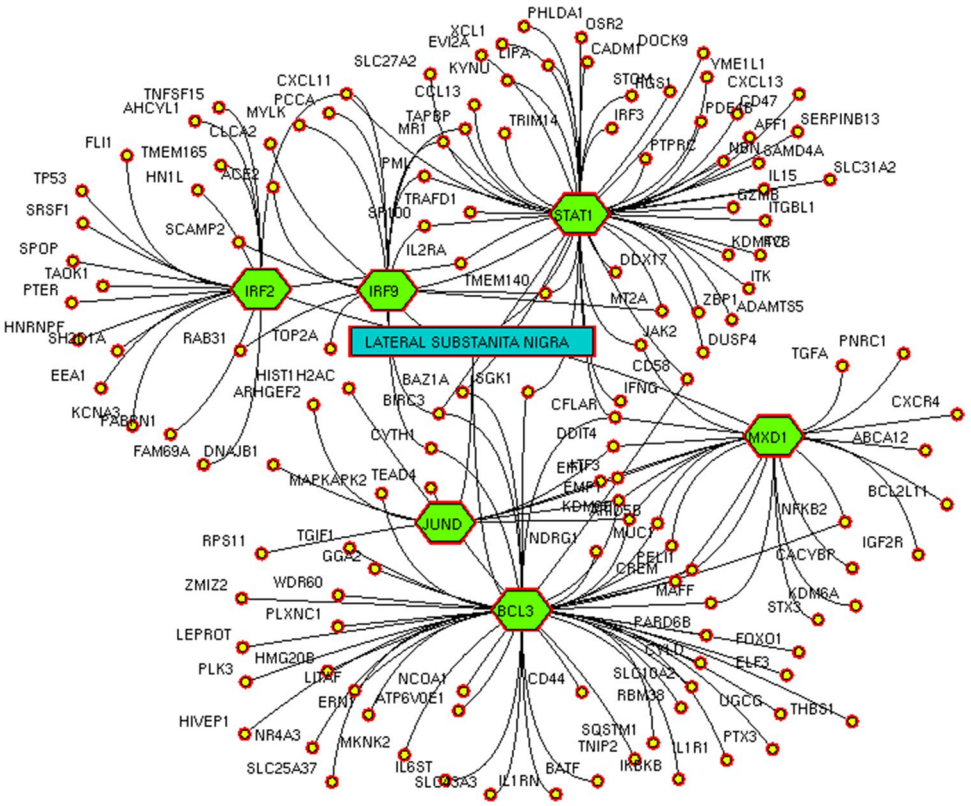

Fig. 3 Regulatory network in lateral substantia nigra. Network representing the transcription factors (green polygon) regulating (back dotted edges) the up-regulated genes (yellow ellipse) in Parkinson's disease

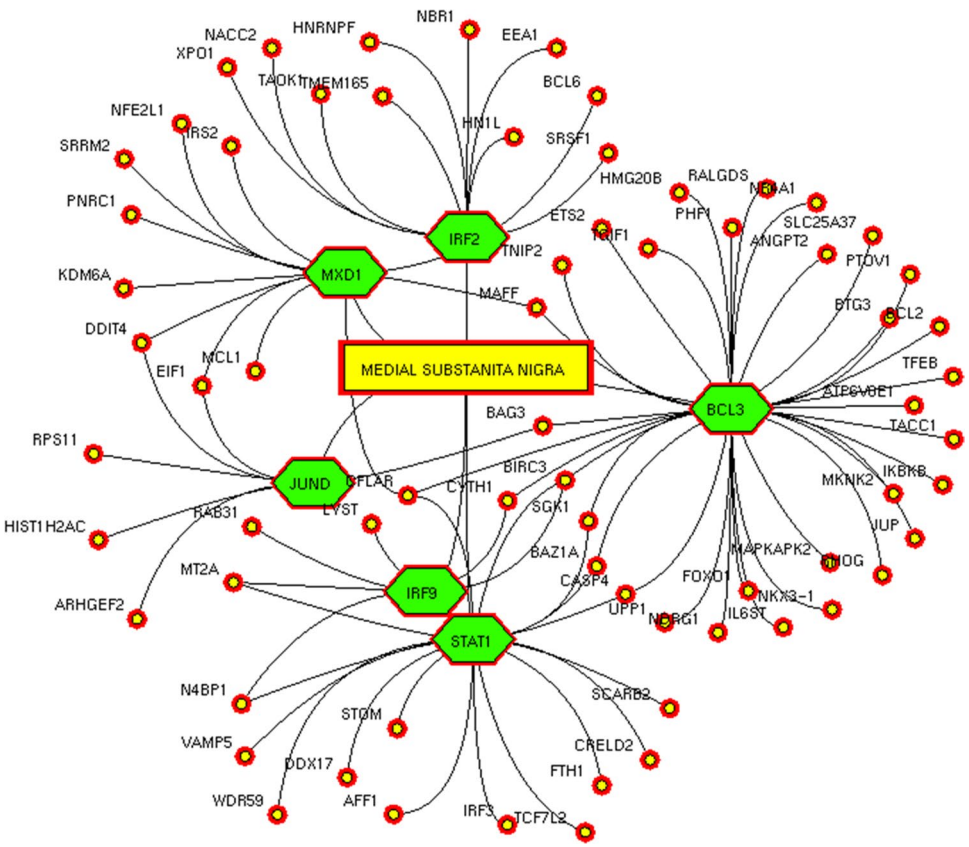

Fig. 4 Regulatory network in medial substantia nigra. Network representing the transcription factors (green polygon) regulating (back dotted edges) the up-regulated genes (yellow ellipse) in Parkinson's disease

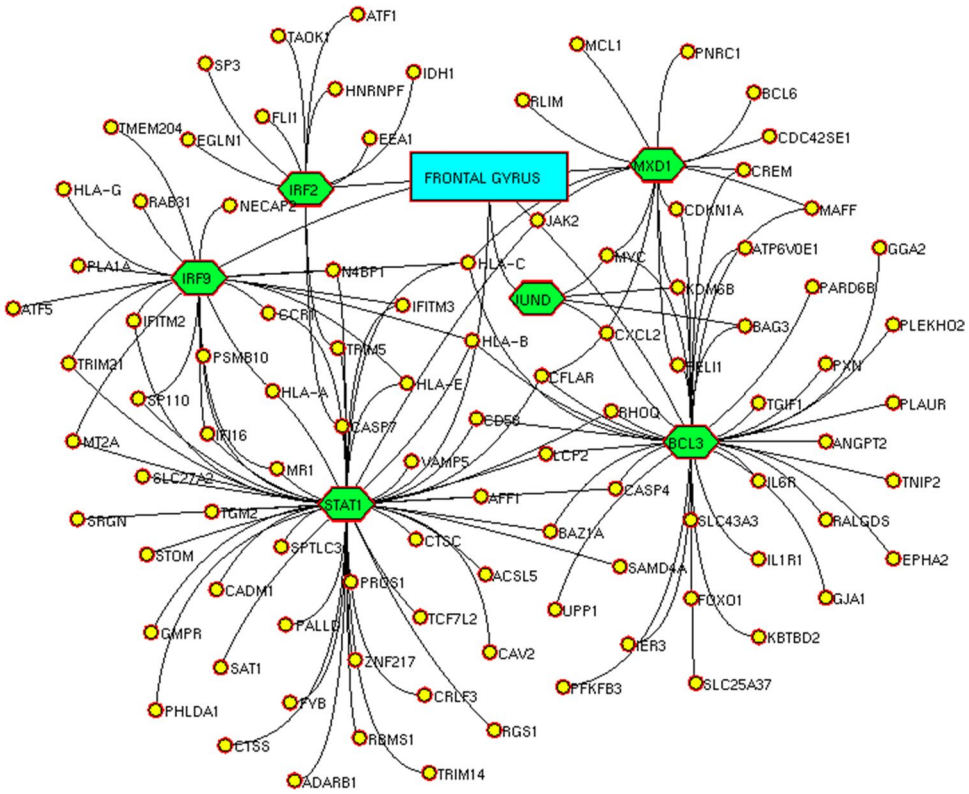

Fig. 5 Regulatory network in the frontal gyrus. Network representing the transcription factors (green polygon) regulating (back dotted edges) the up-regulated genes (yellow ellipse) in Parkinson's disease

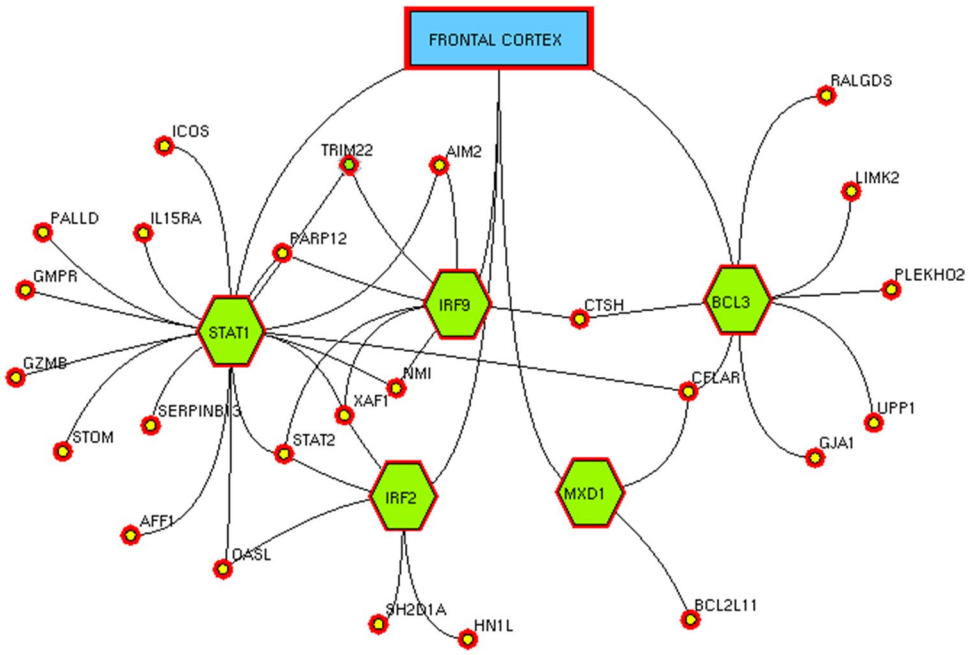

Fig. 6 Regulatory network in the frontal cortex. Network representing the transcription factors (green polygon) regulating (back dotted edges) the up-regulated genes (yellow ellipse) in Alzheimer's disease

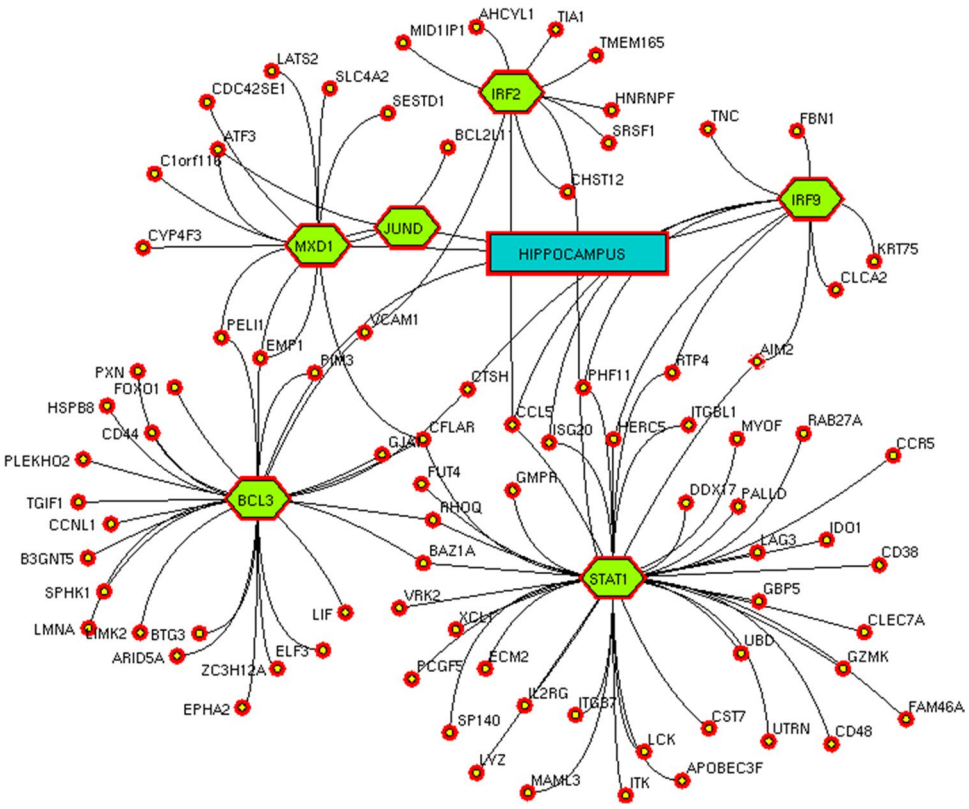

Fig. 7 Regulatory network in the hippocampus. Network representing the transcription factors (green polygon) regulating (back dotted edges) the up-regulated genes (yellow ellipse) in Alzheimer's disease

SP140L, BCL3, STAT4, NFKBID, TRIM22, JUND, STAT1, BLOC1S1, SP110, TRIM38, MXD1, SP140, and HESX1) encoding mRNA over-represented on COVID-19 infection in lungs. Most of these transcription factors play a vital role in the host viral defense mechanism. Mainly, IRF2 and IRF9 are members of the interferon (IFN) regulatory factors involved in regulating interferon system with TRIM22 and STAT1 as anti-viral and anti-bacterial components [46, 47]. The IRF9 regulates inflammation and immune cell in autoimmune disease [48–50]. TRIM22 is the component of TRIM family involved in apoptosis, immune signaling, and antiviral activities [50]. Interestingly, TRIM22 restricts the

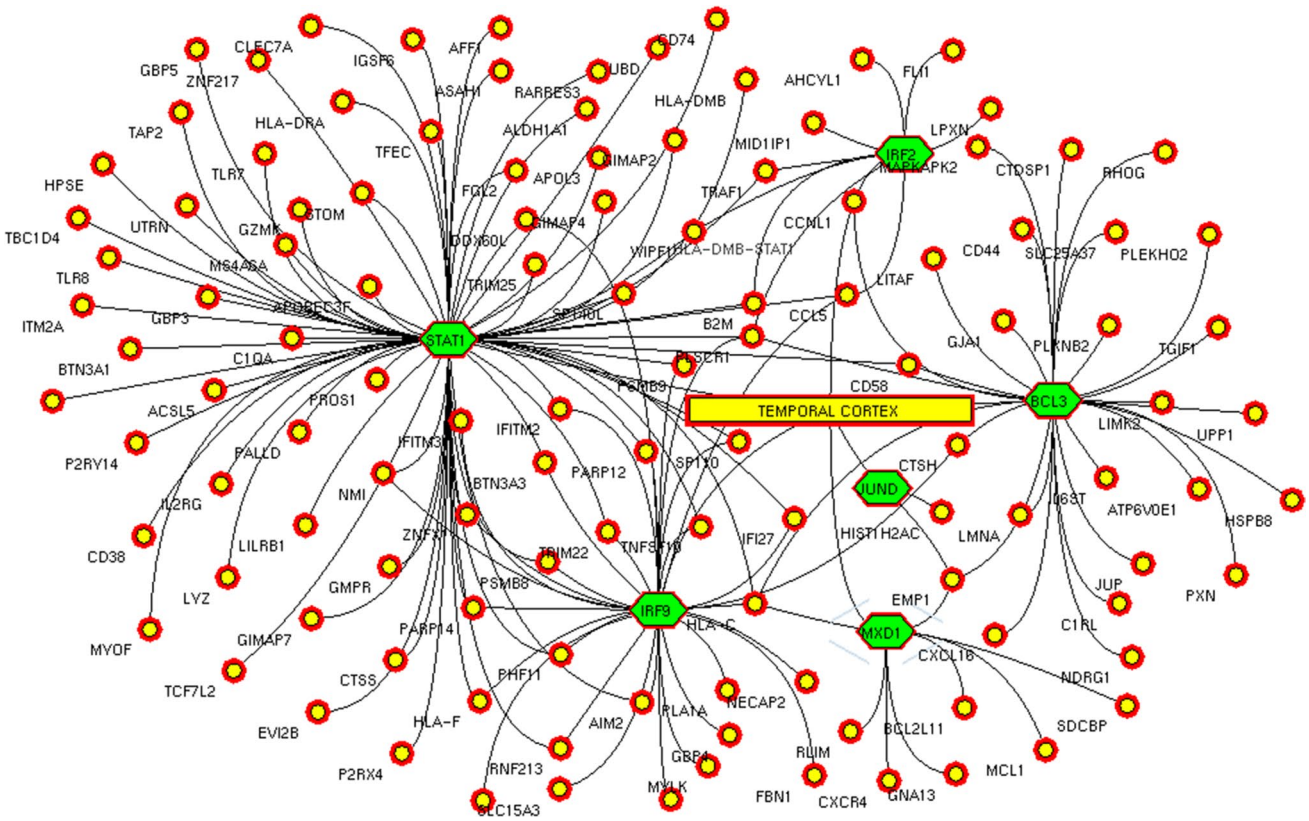

Fig. 8 Regulatory network in the temporal cortex. Network representing the transcription factors (green polygon) regulating (back dotted edges) the up-regulated genes (yellow ellipse) in Alzheimer's disease

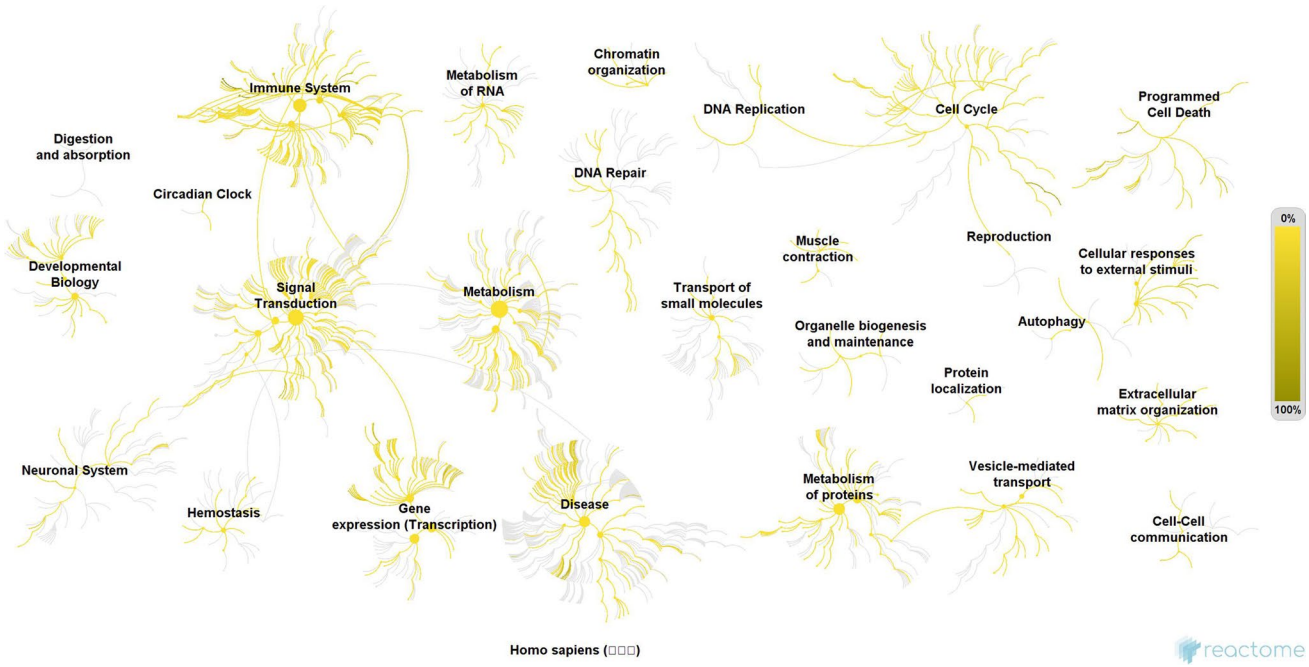

Fig. 9 Functional enrichment of Parkinson's disease genes regulated by the transcription factors. Transcription factors activating PD genes showing major involvement in the immune system, signal transduction, cell cycle, and programmed cell death

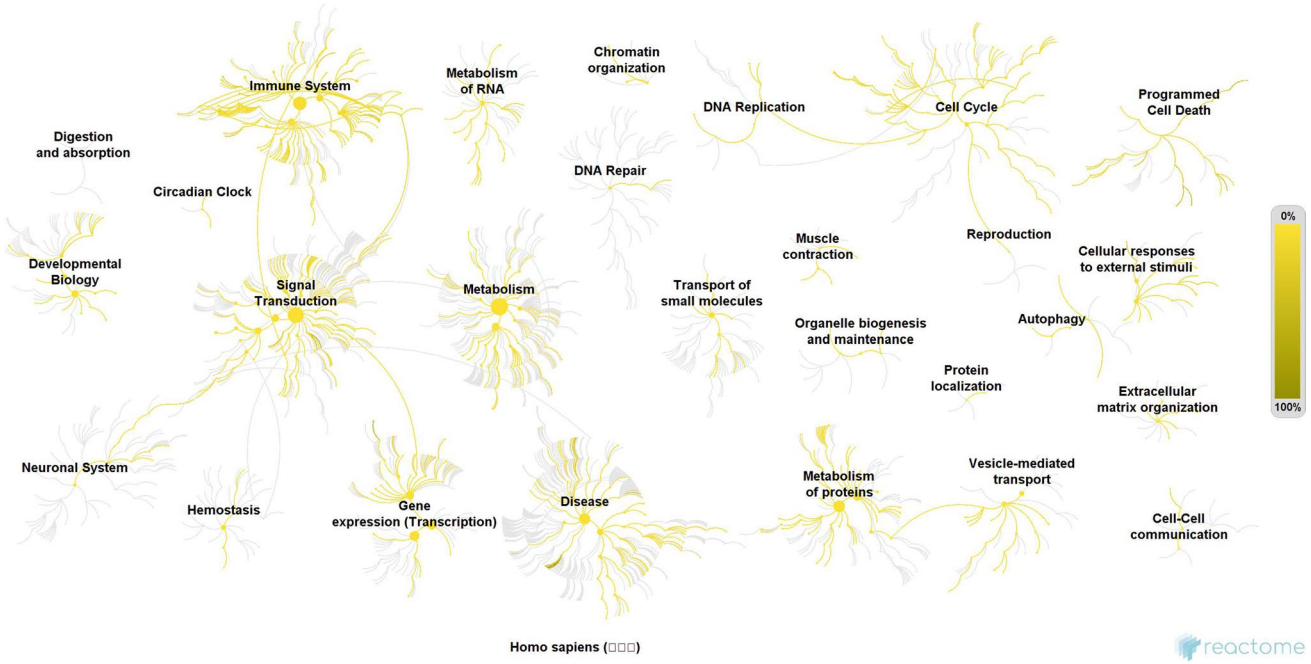

Fig. 10 Functional enrichment of Alzheimer's disease genes regulated by the transcription factors. Transcription factors activating AD genes showing significant involvement in the immune system, signal transduction, metabolism, cell cycle, and response to external stimuli

replication of various viruses, including HIV, hepatitis B virus, and influenza A virus [51–53]. Likewise, MXD1 is the MAX dimerization protein 1 transcription factor regulating cell differentiation, proliferation, and apoptosis. MXD1 was noticed up-regulated in $CD14^+$ monocytes and $CD4^+$ T cells on COVID-19 infection [54]. Recently, Mamoor et al. demonstrate the role of MXD1 in host cells' response to COVID-19 infection [55]. Also, Howard et al. reported the influence of MXD1 expression upon H1N1 and H9N2/G1 viral infection in the host [56]. Furthermore, silencing of MXD1 decreases the H9N2 replication process [56]. Similarly, PHF11 is one of the interferon-stimulated genes expressed by a host on viral infections that regulates cytokine genes in T lymphocytes [57, 58]. A study reports enriched cytokines and chemokines in HIV-infected patients' exosomes compared to HIV-negative control [59]. Similarly, lipopolysaccharide (LPS) stimulated RAW 264.7 cells to produce exosomes with increased chemokine and RNA molecules involved in regulating inflammation [60].

Herein, our RNA-Seq analysis of the GSE121307 dataset showed 19 TFs in the lung-derived exosomes on COVID-19 infection. The lung exosome interacts with brain microvascular endothelial cells that anatomically connect the pathological hotspot of neurodegenerative diseases like AD and PD. The exosomal connectivity between the lungs to BBB and BBB to other neuronal regions was determined based on literature [27–32]. Exosomal delivery of 19 TFs encoding mRNAs to the neuronal hotspot may get translated into proteins using translational machinery of target cells. Timothy et al. report the functional activity of translated exosome-shuttled mRNA in the target cells [61]. Similarly, Montecalvo et al. and Corrado et al. reported the change in molecular pathways in the target cells on the transfer of exosomal cargoes [62, 63]. Also, Valadi et al. report the cellular modulation in target cell on translating the exosomal mRNA into proteins by the target cell translational machinery [64]. Particularly, Valadi et al. demonstrated the support of translational machinery for the protein synthesis of exosome-transported mRNAs in the target cells using in vitro translation assay [64].

In the present study, we demonstrated that the translation of these 19 transcription factors will activate their target genes. Among these, six TFs were noticed activating 469 genes associated with AD and PD on binding to their regulatory regions. Most of these activated genes are involved in inflammatory, apoptosis, and other signal transduction processes that contribute to the neurodegeneration process. Although our study identified novel information about the transcription factors regulating neurodegenerative genes on COVID-19 infection, few limitations need to be considered. First, the identified transcriptional regulatory networks were derived using a heterogeneous dataset. Second, no functional exploration was made to understand the significant regulatory network based on COVID-19 infection. Third, difference in regulatory behavior of the network based on gender was not established due to limited samples in dataset that

avoid sub-group analysis. Alternatively, the strength of this study need to be acknowledged: (1) This study presents a novel approach of integrating multiple datasets to understand the pathogenesis caused by exosome communication in COVID-19. (2) To the best of knowledge, this is the first study to present a unique exosome communication model that aids in understanding the impact of peripheral exosome on the CNS.

Conclusions

In conclusion, our study explores the behavior of exosomal TF regulating PD and AD causative genes at neuronal regions on SARS-CoV-2 infection. Although the public repository data were used, we implemented several curation levels to achieve the pathologically relevant TF regulatory network associated with neurodegenerative diseases. More particularly, the step-wise procedure implemented in the present study was strategically confirmed at each stage of methodology with biological and literature evidence. With the rapidly enlarging COVID-19 pandemic, there is an unprecedented level of impact on the research sector and access to laboratory work. Therefore, many research investigations are underway to utilize the publicly available data on SARS-CoV-2 to expand the research efforts to handle the present critical situation. On this basis, the present study enhances the knowledge of COVID-19 influencing neuronal pathogenesis that describes the previously unknown mechanism of the COVID-19 pandemic. However, our hypothesis warrants further investigation.

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Author Contribution S.S.S.J.A.: conceptualization, investigation, writing—original draft. P.P., M.K., A.S., R.M.: investigation. S.R.: manuscript draft correction.

Data Availability The datasets GSE121307, GSE8397, and GSE36980 used in this study are available online at NCBI (https://www.ncbi.nlm.nih.gov/).

Declarations

Ethics Declarations Not applicable

Consent to Participate Not applicable

Consent for Publication The manuscript contains no individual person's data in any form.

Competing Interests The authors declare no competing interests.

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