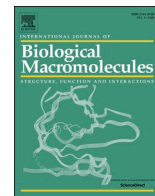




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The SARS-CoV-2 targeted human RNA binding proteins network biology to investigate COVID-19 associated manifestations

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ABSTRACT

The global coronavirus disease 2019 (COVID-19) pandemic caused by the SARS-CoV-2 virus has had unprecedented social and economic ramifications. Identifying targets for drug repurposing could be an effective means to present new and fast treatments. Furthermore, the risk of morbidity and mortality from COVID-19 goes up when there are coexisting medical conditions, however, the underlying mechanisms remain unclear. In the current study, we have adopted a network-based systems biology approach to investigate the RNA binding proteins (RBPs)-based molecular interplay between COVID-19, various human cancers, and neurological disorders. The network based on RBPs commonly involved in the three disease conditions consisted of nine RBPs connecting 10 different cancer types, 22 brain disorders, and COVID-19 infection, ultimately hinting at the comorbidities and complexity of COVID-19. Further, we underscored five miRNAs with reported antiviral properties that target all of the nine shared RBPs and are thus therapeutically valuable. As a strategy to improve the clinical conditions in comorbidities associated with COVID-19, we propose perturbing the shared RBPs by drug repurposing. The network-based analysis presented hereby contributes to a better knowledge of the molecular underpinnings of the comorbidities associated with COVID-19.

1. Introduction

RNA-binding proteins (RBPs), characterized by their binding to single or double-stranded RNA and forming ribonucleoprotein complexes, represent an important troop of post-transcriptional regulators [1]. Proteome-wide studies have established a comprehensive catalog of human RNA Binding Proteins (RBPs) that count up to at least 1200 verified RBPs [2]. By and large, RBPs control all different aspects of RNA fate and function such as RNA splicing, biogenesis, localization, stability, transport, and translation [3]. However, dysregulation of RBPs function by abnormal modifications or genetic mutations may underlie a broad spectrum of human pathologies including diabetes, cardiovascular disease, and other disorders such as cancer and neurodegenerative diseases [4,5]. The virus responsible for the latest menace COVID-19, the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), relies on host cellular RBPs to replicate and increase its numbers within the human body [6]. SARS-CoV-2's pathogenic success depends on its ability to repurpose host RBPs and to evade antiviral RBPs. While SARS-

CoV-2 or other viruses hijacks cellular RBPs [7,8], as a counteract the host cell employs specialized RBPs to detect viral RNAs [9] triggering the cellular antiviral state, characterized by suppressed viral gene expression through the inhibition of protein synthesis and the production of interferons. These mechanisms make cellular RBPs critical regulators of the virus life cycle, either promoting or restricting infection [8,9].

More than 360 million confirmed cases of COVID-19 and more than five million associated deaths have been reported around the globe by end of January 2022 (<https://COVID-19.who.int>). In general, SARS-CoV-2 is associated with significant respiratory and pulmonary complications, causing pneumonia and acute respiratory distress syndrome (ARDS). However, in many cases, manifestations of COVID-19 that are not pulmonary such as renal, hepatobiliary, endocrinological, gastrointestinal, cardiovascular, hematologic, dermatological, ophthalmological, and neurological systems have also been reported [10–12]. As a matter of fact, comorbidities like hypertension, diabetes, renal disease, cancer, cardiovascular disease, and HIV have been identified as risk

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factors for death in COVID-19 patients [13]. Amassing proof from many recent studies also links neurological indications like headaches, nausea, consciousness impairment, seizures, anorexia, anosmia, encephalopathy, encephalitis, ischemic and hemorrhagic stroke, acute motor axonal neuropathy (AMAN), and acute inflammatory demyelinating polyneuropathy (AIDP) to COVID-19 [14–18].

To date, several human-SARS-CoV2 interactomes have been created which aid in comprehending the viral entry, infection, and disease development mechanisms [19–23]. Analysis of these networks has revealed commonalities and distinctions based on genes and molecular pathways associated with viral pathogenicity. The functional data provided by advances in the mapping of the human-SARS-CoV2 interactome network, as well as in the systematic identification of gene-disease associations, could be exploited for exploring fundamental connections between viral targets and disease genes.

In the current study, we have utilized a network-based systems biology approach to investigate the RBPs-based molecular interplay between COVID-19, various human cancers, and neurological disorders. Firstly, a protein-protein interaction network of the 91 human RBPs, targeted by SARS-CoV-2 delineated by Schmidt and co-workers [19] has been constructed which displays highly complex interconnectivity among these RBPs. Further using these RBPs, we identified the associated neurological diseases to produce a disease-RBPs interaction network to understand the link between the COVID-19 targeted RBPs and neurological disorders. Furthermore, we obtained a network based on common RBPs involved in COVID-19, cancers, and brain disorders. This network consists of 9 RBPs connecting 10 different cancer types, 22 different brain disorders, and COVID-19 ultimately hinting at the comorbidities and complexity of COVID-19 infection. Next, we have explored the miRNA regulatory interactions of these 9 RBPs. Finally, we propose the shared RBPs of the three conditions to be the potential candidates for drug repurposing with the higher aim to ameliorate medical conditions in comorbidities associated with COVID-19.

2. Materials and methods

2.1. Generation of PPI network of SARs-Cov2 affected RBPs

The list of 91 RNA Binding Proteins (RBPs) interacting with COVID-19 viral proteins was retrieved from Schmidt et al. study [19]. The Protein-Protein interaction network of the selected RBPs was constructed using the STRING plugin of the Cytoscape tool (version: 3.8.2) [24]. For preparing the PPI network, the STRING [25] plugin uses text-mining data, gene fusion, co-expression, neighborhood, and experimental data.

2.2. Calculation of topological properties of the PPI network

The topological properties of the network were calculated as we did in our previous studies [21,26] using the network analyzer plugin of Cytoscape. The calculated network topological properties include the degree of centrality (k), betweenness centrality, closeness centrality, and topological coefficient values for identifying the highly connected nodes.

Degree of centrality (k) signifies the number of interactions made by nodes in a network and is expressed as:

$$\text{Degree centrality } (k) = \sum_{a \in K_u} w(a, b)$$

where, K_u is the node-set containing all the neighbors of node a , and $w(a, b)$ is the edge weight connecting node a with node b .

Betweenness centrality (C_b) represents the degree to which nodes stand between each other based on the shortest paths. A node with higher betweenness centrality represents more control over the network. It is expressed as:

$$C_b(u) = \sum_{k \neq u \neq f} \frac{p(k, u, f)}{p(k, f)}$$

where $p(k, u, f)$ is the number of interactions from k to f that passes through u , and $p(k, f)$ denotes the total number of shortest interactions between node k and f .

Closeness centrality (C_c) is a measure of how fast information is traveled from one node to other nodes in the network. Closeness centrality value ranges from 0 to 1, isolated genes have closeness centrality value equal to zero.

$$C_c(z) = \frac{1}{\text{avg}(L(z, m))}$$

where z is the node for which the closeness value is calculated and $L(z, m)$ is the length of the shortest path between two nodes z and m . It has been seen, genes having a high degree of connectivity also have high closeness centrality score.

Topological coefficients (T_f) indicate the tendency of the nodes in the network to have shared neighbors. Nodes having no or one neighbor are assigned a topological coefficient of zero. The topological coefficient of a node, n with k_f neighbors is computed as:

$$T_f = \frac{\text{avg}(j(f, p))}{k_f}$$

where $j(f, p)$ is the number of shared neighbors between f and p , plus 1 if there is an edge between f and p .

2.3. Constructing brain-specific disease-gene interaction network

After obtaining the list of COVID-19 affected RBPs, Disease-gene interaction databases such as GeneORGANizer, DisGeNET, and MalaCards databases [27–29] were screened to identify the brain-related disorders linked with the concerned RBPs. These databases allow us to analyze the relationship between the genes and the organs affected by them. A total of more than ~2 million disease-gene interactions were retrieved from these databases, of which disease-gene interactions specifically related to the brain and the concerned RBPs were further sorted and retrieved using in-house Perl script.

2.4. Identification of commonly involved RBPs in COVID-19, cancer and brain disorders

A list of RBPs showing dysregulation among 15 different types of cancers was retrieved from Wang et al. study [30]. For identifying the common RBPs in COVID-19, neurodegeneration, and cancer, InteractiVenn [31], a web-based tool was used to analyze the gene sets through the Venn diagram. As query genes sets, a list of 91 RBPs playing role in brain-related disorders and cancers was used. Enricher Database was used to identify the change in gene expression of the commonly identified RBPs by Covid-19 viral infection.

2.5. Gene ontology and pathways enrichment analysis

Database for annotation, visualization, and integrated discovery (DAVID) [32] was used for the comprehensive enrichment analysis of the RNA binding proteins. DAVID uses GO and Kyoto encyclopedia of genes and genomes database (KEGG) [33] for functional and pathways enrichment analysis. Functional enrichment analysis includes analysis at biological, cellular, and molecular levels. The pathways and functions having P -value < 0.05 were considered significantly enriched and were used further in the study.

2.7. Identification of drugs as a modulator

Enrichr database [40] was screened to identify the drugs showing interaction with the selected RBPs. Enrichr is a Gene Set Enrichment Analysis (GSEA) based web tool, which accumulated knowledge about the function of the group of genes. Enrichr in the back-end scanned

multiple drug-gene interaction databases along with gene expression omnibus (GEO) database and provides the related significant interactions.

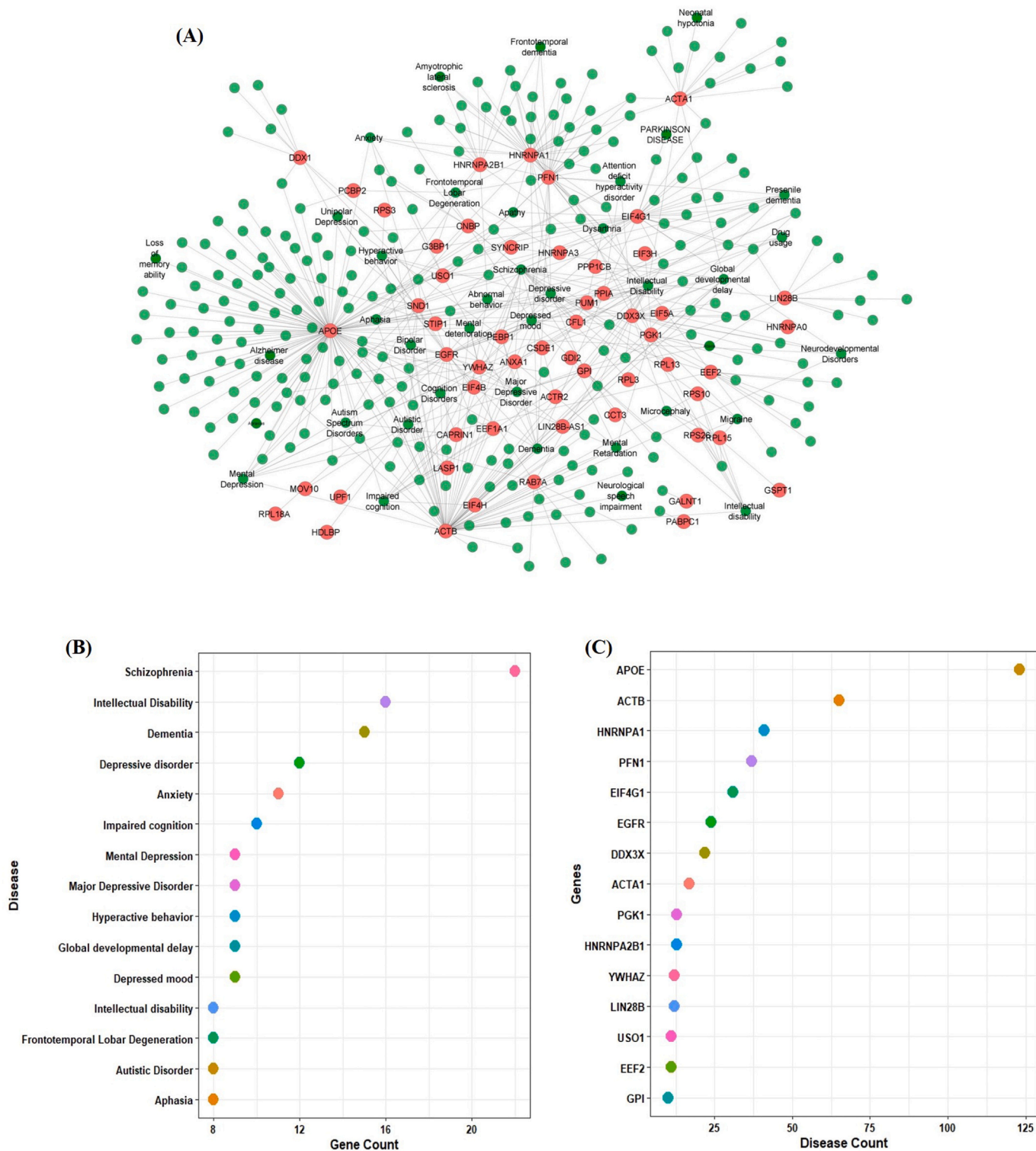


Fig. 2. SARS-CoV-2 targeted RBPs-disease interaction network in the brain. (A) SARS-CoV-2 targeted RBP gene (red) interaction network in the human brain with neighbouring diseases (green). (B) Dot plot of highly connected diseases along with the number of RBPs connected to the brain in the disease-gene interaction network. (C) Dot plot of highly connected RBPs to various brain diseases in the network.

3. Results

3.1. Protein-protein interaction network of COVID-19 targeted host RBPs

For constructing the human RBPs-SARS-CoV-2 interactome, the list of 91 RBPs was used as query gene set in the STRING plugin of Cytoscape tool (Version: 3.8.2) (Supplementary Table 1). The network prepared showed a very high number of interactions among RBPs (Fig. 1A, Supplementary Table 2). To further strengthen the above statement, we calculated the eccentricity value of the network. The eccentricity of a node in a biological network can be interpreted as the easiness of the node to be functionally reached by all other nodes in the network. The

nodes having a high eccentricity value as compared to the average eccentricity value of the network can influence other nodes in the network more easily and vice-versa and can also be easily influenced themselves. We observed that >88 % of the nodes in the network had high eccentricity value than the average eccentricity value (i.e., 3.8), suggesting that the functionality of the nodes in the network was highly linked to each other. PABPC1 (k = 58), EEF2 (k = 55), EEF1A1 (k = 52), EIF4G1 (k = 50) and HNRNPA1 (k = 46) were the top 5 most connecting RBPs in the network with high degree of connectivity (k) and betweenness centrality value.

Gene Ontology analysis of the 91 RBPs using the DAVID tool reveals that these RBPs were significantly enriched in translational initiation,

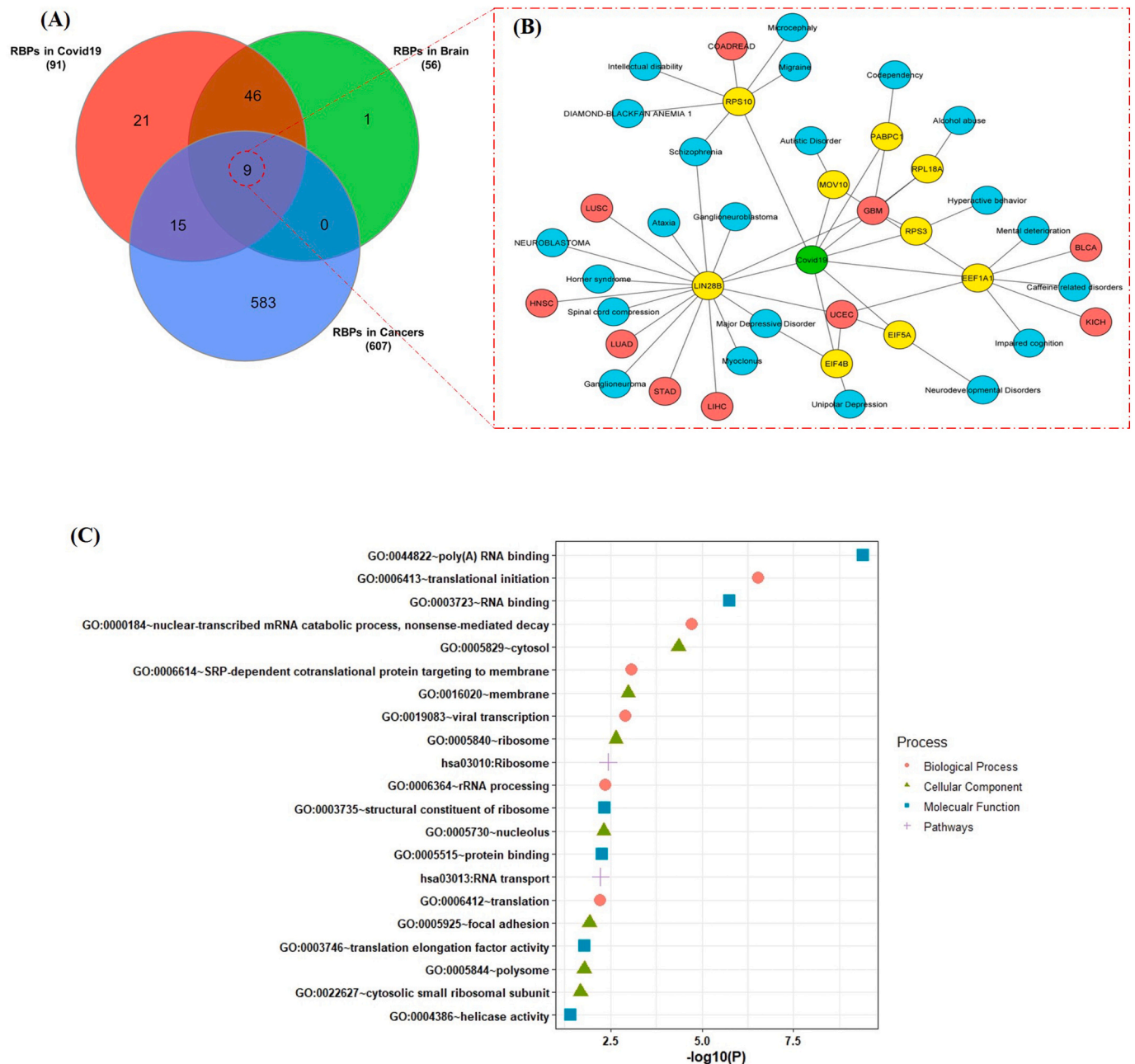


Fig. 3. Disease-gene interactions. (A) Venn diagram for identifying the RBPs commonly shared in COVID-19, brain-related disorders, and cancers. The list of 91 RBPs interacting with SARS-CoV-2 proteins was retrieved from Schmidt et al. [19]. Out of 91 RBPs, 56 RBPs showed interaction with 278 different brain-related disorders using several disease-gene interaction databases. The list of 607 RBPs showing dysregulated in 15 different types of cancers was retrieved from Wang et al. [30]. (B) PPI network of commonly shared nine RBPs (yellow) in COVID-19 (green), cancer (red), and neurological disorders (blue). (C) Gene ontology and pathway enrichment analysis of nine shared RBPs.

Viral transcription, translation, rRNA processing, cell-cell adhesion, and formation of the translational preinitiation complex. Moreover, the selected RBPs were enriched in the membrane, intracellular ribonucleoprotein complex, cytosol, focal adhesion, cell-cell adherens junction, and cytoplasmic stress granules. Whereas, based on the molecular functions, these RBPs were enriched in poly(A) RNA binding, RNA binding, cadherin binding involved in cell-cell adhesion, protein binding, and nucleotide-binding (Fig. 1B, Supplementary Table 3). Pathway's enrichment analysis revealed the role of RBPs in the ribosome, RNA transport, mRNA surveillance pathway, regulation of actin cytoskeleton, oxytocin signaling pathways, and proteoglycans in cancer pathways (Fig. 1C, Supplementary Table 3).

3.2. Disease-RBP interaction network specific to brain

A disease-RBP interaction network was prepared to understand the link between the COVID-19 target RBPs and neurological disorders. For constructing the network several disease-gene interaction databases were screened. These databases help analyze the relationship between the genes and the organs affected by them. Out of 91 RBPs, 56 RBPs showed interaction with 278 different brain-related disorders, making a network having 561 disease-RBP interactions (Fig. 2A, Supplementary Table 4). The network showed that several brain disorders were connected with more than one gene in the network such as Schizophrenia ($k = 22$), Intellectual Disability ($k = 16$), Dementia ($k = 15$), Depressive disorder ($k = 12$), and Anxiety ($k = 11$) (Fig. 2B, Supplementary Table 5). Similarly, the network also reveals that many of the disorders also share common genotypes, for example, APOE ($k = 123$), ACTB ($k = 65$), HNRNPA1 ($k = 41$), PFN1 ($k = 37$), and EIF4G1 ($k = 31$) are linked to multiple brain disorders (Fig. 2C, Supplementary Table 6).

3.3. Identification of commonly involved RBPs in COVID-19, cancer and brain disorders

Apart from the list of 91 COVID-19 target host RBPs including 56 RBPs playing role in neurological disorders, we have also retrieved the list of 607 RBPs showing dysregulation among 15 different types of cancers as reported by Wang et al. [30]. Venn-based analysis of the 3 sets of genes revealed 9 common RBPs, namely EEF1A1, EIF4B, EIF5A, LIN28B, MOV10, PABPC1, RPL18A, RPS10, and RPS3 involved in COVID-19, cancer, and neurological disorders (Fig. 3A). Out of 9 identified RBPs, 3 RBPs (EIF4B, MOV10, and RPS3) also can form stress granules.

Gene Ontology analysis of these commonly identified RBPs revealed translation initiation, nuclear-transcribed mRNA catabolic process, nonsense-mediated decay, viral transcription, rRNA processing, and translation as the most enriched biological process. In the cellular component, the RBPs were enriched in the cytosol, membrane, ribosome, nucleolus, focal adhesion, and cytosolic small ribosomal subunit. Whereas, the molecular functions were enriched in poly(A) RNA binding, RNA binding, protein binding, structural constituent of ribosome, and helicase activity. Pathway's enrichment analysis reveals the role of RBPs in mainly two pathways i.e., ribosome and RNA transport pathways (Fig. 3B, Supplementary Table 7).

Further the commonly identified RBPs were screened for their change in expression by Covid-19 viral infection using the Enrichr database [40]. Out of the 9 commonly identified RBPs, we identified the increase in the expression of 5 RBPs (namely RPS3, RPS10, EIF4B, EEF1A1 and EIF5A) after the Covid-19 viral infection (Supplementary Table 8).

3.4. MicroRNAs as a regulator for commonly identified RBPs

MicroRNAs (miRNAs) are small non-coding RNAs regulating the expression of genes by interacting with the target mRNAs. miRNAs play important role in many viral diseases such as Ebola, SARS, and HIV by

downregulating the host's gene [55]. These properties make miRNAs a potential therapeutic target. For identifying the miRNA interacting with the commonly selected 9 RBPs, several miRNA-gene interaction databases were screened. A total of 492 miRNAs were identified showing possible interaction with the concerned RBPs. A list of 149 miRNAs having antiviral properties was retrieved from the VIRmiRNA database. Out of 492 miRNAs interacting with the commonly identified RBPs, 97 miRNAs were shown to have antiviral properties according to the VIR-miRNA database. A network of 492 miRNAs, 9 RBPs, and 739 miRNA-RBPs interaction was prepared using the Cytoscape tool (Supplementary Fig. 1, Supplementary Tables 9–10).

We have calculated the topological parameters of the network created with antiviral miRNAs and the concerned RBPs. Interestingly, the top 5 miRNAs having a high degree of connectivity and betweenness centrality values show interaction with all the concerned 9 RBPs showing their role in cancer, COVID-19, and neurologically related disorders (Fig. 4A). These 5 miRNAs can be considered and further studied as a potential therapeutic target.

Gene ontology analysis of the selected 5 antiviral miRNAs revealed that the biological process is enriched in positive regulation of gene expression, positive regulation of the metabolic process, response to stimulus, positive regulation of the cellular metabolic process, regulation of signal transduction, and regulation of cell migration. In the cellular component, miRNAs were enriched in extracellular space, extracellular exosome, extracellular vesicle, and membrane-bound organelle. Whereas molecular function was enriched in RNA binding, mRNA binding, nucleic acid binding, and organic cyclic compound binding (Fig. 4B). Pathway's enrichment analysis revealed their role in Metabolic pathways, RIG-I-like receptor signaling pathways, Non-alcoholic fatty liver disease, Amino sugar, nucleotide sugar metabolism, Wnt signaling pathways, folate biosynthesis, and Ras signaling pathways (Fig. 4C, Supplementary Table 11).

3.5. Drug repurposing

For identifying the drug molecules interacting with the concerned RBPs, the Enrichr database was screened. The GSEA of the drug perturbations from GEO database records of downregulated genes revealed pioglitazone and lapatinib as the top significant enriched candidates (Supplementary Fig. 2). Pioglitazone seems to affect 6 RBPs out of 9, whereas lapatinib affects the 3 RBPs. These observations thus provide initial evidence that both of these drugs can be considered for drug repurposing. Next, we scanned the GEO profiles related to both the drugs on the NCBI database and interestingly identified that together pioglitazone and lapatinib decreases the expression of the 5 RBPs whose expression were being upregulated after the covid-19 infection. Pioglitazone decreases the expression of RPS3, eIF4B, and RPS10 (Supplementary Fig. 3A), similarly lapatinib also decreases the expression of EEF1A1, EIF5A, and RPS10 RBPs (Supplementary Fig. 3B).

4. Discussion

SARS-CoV-2 possesses a positive-sense, single-stranded, monopartite RNA genome [41]. Such viruses are known to co-opt host RNA-binding proteins (RBPs) for diverse processes including viral replication, translation, viral RNA stability, assembly of viral protein complexes, and regulation of viral protein activity [42,43]. The identification of the RBPs that bind to viral transcripts thus becomes important for revealing the molecular rewiring of viral gene regulation and the activation of antiviral defense systems.

Recent research has shown that cancer increases COVID-19 susceptibility and is a risk factor for poorer clinical outcomes in COVID-19 patients [20,44–50]. Among 1590 instances with COVID-19 in China, Liang et al. reported a cancer prevalence of 1.13 % [95 % confidence interval (CI): 0.61 %–1.65 %], which was greater than the overall cancer incidence of 0.29 % in Chinese population. [51]. Furthermore, a meta-

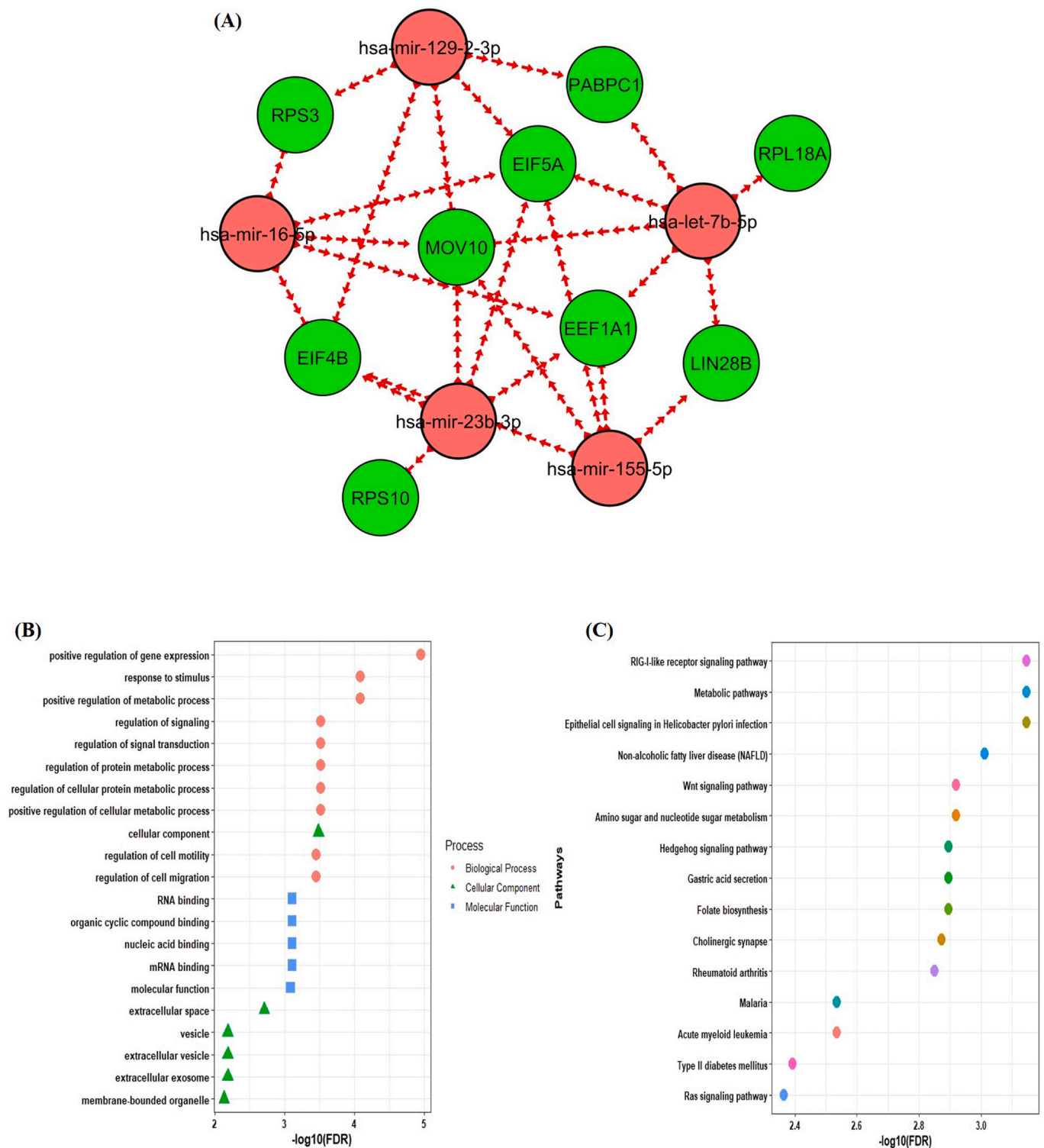


Fig. 4. miRNA-protein interaction network. (A) Interaction network of top five miRNAs selected based on the high degree of connectivity with the nine shared RBPs. (B) Gene Ontology analysis of the antiviral miRNAs interacting with key SG genes. (C) KEGG pathways enrichment analysis of antiviral miRNAs.

analysis based on outcomes of 46,499 COVID-19 patients with malignancies demonstrated that all-cause mortality was higher in patients with cancer than in people without cancer (Risk Ratio (RR): 1.66, 95% CI: 1.33–2.07, $P < 0.0001$) [46]. A while back, Yang et al. [104] conducted a meta-analysis based on 19 clinical studies across 9 countries (China, Iran, Italy, Portugal, Republic of Korea, Spain, Switzerland, UK, and USA) that included 63,019 participants concluding that patients with cancer are more susceptible to COVID-19. Cancer was found to

increase mortality among COVID-19 patients as a risk factor. Lung cancer patients showed a higher mortality rate than patients without lung cancer among COVID-19 cancer patients. The authors concluded that patients with cancer are more likely to develop a serious COVID-19 infection. [52]. Also, in COVID-19 patients, encephalopathy significantly contributes to morbidity. [53,54]. A cross-sectional study based on 355 patients indicated that COVID-19 neurologic problems affect 7% to 69% of patients with severe infection, which is much more common

than was previously thought. Emerging hospital records show that the neurologic impairment is usually linked to acute respiratory infection with SARS-CoV-2. Most infected people experience mild neurologic symptoms such as headaches, early anosmia, and dysgeusia, which usually resolve [56]. More critically ill patients with hypoxic respiratory failure seem to experience more severe sequelae, which can be fatal to those who are particularly vulnerable. These problems include extended delirium, convulsions, and meningoencephalitis [17]. Quite understandably, owing to their baseline immunocompromised state and inadequate functional reserve, cancer patients are particularly at risk of developing serious infections from COVID-19 [57]. Therefore, it is crucial to comprehend the biology of COVID-19's neurologic effects on the community of cancer patients. Besides this, Remsik J et al. hinted at the involvement of neuroinflammatory process(es) in neurologic complications of COVID-19 infection in their prospective analysis of clinical neurologic characterization of cancer patients with neurologic toxicity following SARS-CoV-2 infection (that corroborated with biochemical analysis of CSF) [58]. Intrigued by the occurrence of neurological disorders and cancer subtypes as comorbid conditions of COVID-19 disease as well as RBPs being the shared component, we adopted an integrative network biology approach to decipher the RBP-based molecular alliance of COVID-19 with neurological disorders and various types of cancers. Our results of the PPI network of COVID-19 affected RBPs indicate that these RBPs operate in a highly interconnected network that coordinates many activities of the cellular RNA homeostasis. In the brain-specific disease-RBP network obtained from analyzing COVID-19 affected RBPs only, a disproportionately large number of gene-disease associations could be attributed to a small subset of RBPs and neurological disorders. Diseases such as schizophrenia, intellectual disability, dementia, depressive disorder, and anxiety represented the most connected disease classes based on RBPs, ApoE, and ACTB. ApoE is an important lipoprotein involved in lipid and cholesterol metabolism [59] and has already been reported as the major risk factor for many CNS disorders including Alzheimer's disease [60]. Research studies indicate that the e4 allele of *ApoE* is associated with a higher risk of deep vein thrombosis and has recently been suggested to be an indicator for severe COVID-19 [61]. *ACTB* encodes for the most abundant eukaryotic cytoplasmic protein, β -actin, a reduced amount of which causes an alteration in cell shape, migration, proliferation, and gene expression leading to detrimental effects on kidney, brain, and heart development [62].

The most interesting and significant finding of this study is the identification of 9 shared RBPs that link COVID-19 to neurological disorders and various types of cancers at the molecular level. Among these, Poly(A) Binding Protein Cytoplasmic 1 (PABPC1) is largely involved in RNA degradation, stabilization, and translation enhancement [63,64], and is implicated in multiple viral infections. Herpes simplex virus (HSV), rotaviruses, bunyavirus, and some nonviral stresses such as heat shock, utilize PABPC1 relocalization from the cytoplasm to the nucleus as a means to commandeer cellular resources [65,66]. Recently, Gao et al. speculated that SARS-CoV2 endonuclease NSP15 might target host cell RNA to relocate PABPC1 to the nucleus [67]. Another RBP, MOV10 (Moloney murine leukemia virus infection in mice), an interferon-inducible RNA helicase, is a multifunctional protein and has been implicated in a wide range of cellular functions including RNA silencing, mRNA translation, and polycomb-mediated tumor suppression [68–71]. While some of the MOV10 functions are dependent on its helicase activity and P-body localization [68,72,73], MOV10 exhibits antiviral activity by two possible mechanisms i.e. regulation of antiviral gene expression, possibly through IFN signaling [74] and alteration of miRNA expression directly or indirectly for viral clearance effects [75]. Interestingly, the SARS-CoV2 N protein interacts with the P-bodies components MOV10, and PABPC1 [20], however, the role of these cytoplasmic granules as pro- or anti-viral mechanisms is yet to be established. The RNA remodeler MOV10 tends to bind mRNAs encoding proteins involved in neuron projection, cytoskeleton, and actin-binding, and thus is a potential candidate in neurological disorders like autism and

Alzheimer's disease which pertain to cytoarchitectural causes [76]. Also, MOV10 combined with circ-DICER1 has a silencing effect on the angiogenesis of glioma via miR-103a-3p/miR-382-5p mediated expression regulation of ZIC4 [77]. Further, the translation elongation factor eEF1A1 is a pleiotropic protein that is highly expressed in human tumors, including breast cancer, lung cancer, and ovarian. Besides the canonical role of eEF1A1 in the translation process, its non-canonical roles in promoting oncogenesis, modulation of apoptosis, and viral pathogenesis have also been reported [42,78]. Because of its role in cytoskeleton organisation, eEF1A1 may promote tumor cell motility and spread [79]. Its newly found role in heat shock response makes it a potential target for treating neurodegenerative illnesses where protein folding goes amiss [80,81]. Several RNA viruses utilize eEF1A1 for replication, exploiting varied mechanisms [80,82–86]. The drug plitidepsin exhibits antiviral action against SARS-CoV-2 by inhibiting its recognized target eEF1A [87].

We then mapped the known drug-target network to search for druggable targets among the shared RBPs. The analysis highlighted pioglitazone and lapatinib as the most significant candidates targeting three and six of the nine identified shared RBPs, respectively. Besides being an approved drug for treating the condition of insulin resistance, pioglitazone reduces chronic inflammation in type 2 diabetes patients. Carboni and group [88] proposed that the drug could improve the prognosis in COVID-19 patients with comorbidities such as diabetes, hypertension, and cardiovascular disorders as they have a latent chronic inflammatory state in common. Pioglitazone decreases the expression of three of the shared RBPs, two of those being ribosomal proteins RPS3 and RPS10, which is in line with the fact that pioglitazone therapy restores insulin sensitivity, at least partially, by a coordinated induction of ribosomal protein biosynthesis gene in muscle in PCOS [89]. The other drug targeting the shared RBPs is lapatinib, an FDA-approved drug, which is EGFR/HER2 inhibitor used to treat HER2-positive breast cancer [90,91] and exhibits a good toxicity profile in humans [92]. This drug mainly inhibits tyrosine kinase phosphorylation thereby disrupting the signal transduction pathways of PI3K/Akt and Ras/Raf/MAPK [93]. Remarkably, recent research suggested lapatinib as a novel treatment option for COVID-19 as it inhibited SARS-CoV-2 replication by over 50,000-fold [94].

MiRNAs and RBPs are two of the well-studied post-transcriptional regulators and they may even reciprocally regulate themselves. As part of this study, we have also suggested five miRNAs, which bind and exhibit regulatory effects on the nine shared RBPs and notably these miRNAs also possess antiviral properties. Remarkably, the tolerance to some deadly viruses is attributed to the presence of specific miRNAs in the so-called original host of SARS-CoV-2 i.e. the bats, [95]. Moreover, viruses could utilize the host or their miRNAs to either facilitate viral replication or inhibit the host's antiviral responses [96]. Evidence also suggests that host cellular miRNA(s) can directly target the coding region of the viral genome as well as 3'UTR to induce the antiviral effect. Thus, regulation or manipulation of miRNAs could present a novel basis for antiviral drug therapies. miRNAs have even been considered as drug molecules for targeting the SARS-CoV-2 proteins [97]. Interestingly, two of these five top hit miRNAs targeting the shared RBPs (e.g., hsa-miR-23b-3p, and hsa-miR-155-5p) have been reported to specifically target the SARS-CoV-2 genome as per the study of the Fulzele and group [98]. Very interestingly, 4 of these 5 miRNAs namely, hsa-let-7b-5p, hsa-miR-23b-3p, hsa-miR-155-5p and hsa-miR-129-2-3p have already been implicated in various human cancers [99–103].

5. Conclusion

In summary, our results provide an RBPs-centric view of the involvement of the three diseases, COVID-19, cancer, and neurodegeneration. We here understand the link between the COVID-19 targeted 91 RBPs to the human cancers and neurological disorders through the disease-RBPs interaction network. Thus, these shared RBPs, in

general, have strategic RNA-regulatory functions in cellular pathways that are pathologically altered in COVID-19, cancer, and neurodegenerative diseases. Owing to RBPs pleiotropic nature, their canonical or non-canonical functions, and through regulation of same or different pathways, these RBPs act as a connecting link between these three disease conditions. Understanding the association between COVID-19, cancer and neurological diseases constitutes a fascinating approach to obtaining clues about the underlying pathogenesis and consequently to the development of future therapeutic strategies based on the shared RBPs that present as candidate druggable targets. To the best of our knowledge, this is the first study utilizing a comprehensive and systematic bioinformatics strategy to investigate the shared RBP component hypothesis as a pathogenic mechanism of COVID-19, cancer, and neurological disorders.

CRedit authorship contribution statement

Kartikay Prasad: Conceptualization, Methodology, Data curation, Software. **Pratibha Gaur:** Data curation, Visualization, Writing - Original draft preparation. **Saurabh Raghuvansi:** Software, Validation, Reviewing and Editing. **Vijay Kumar:** Conceptualization, Supervision, Writing, Reviewing and Editing.

Declaration of competing interest

No potential conflict of interest was reported by the authors.

Data availability

The data related to the manuscript are included within the main article and its supplementary files.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijbiomac.2022.07.200>.

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