A network biology approach for identifying crucial host targets for COVID-19

Ranjan Kumar Barman^{1,4#}, Anirban Mukhopadhyay³, Ujjwal Maulik⁴ and Santasabuj Das^{1,2*}

¹Biomedical Informatics Centre, ²Division of Clinical Medicine, ICMR-National Institute of Cholera and Enteric Diseases, Kolkata, West Bengal, India; ³Department of Computer Science and Engineering, University of Kalyani, Kalyani, West Bengal, India; ⁴Department of Computer Science and Engineering, Jadavpur University, Kolkata, West Bengal, India.

The author currently affiliated with the Department of Clinical Hematology at the Tata Medical Center, Kolkata, West Bengal, India.

* Correspondence Author

Dr. Santasabuj Das
National Institute of Cholera and Enteric Diseases (ICMR)
P-33, C.I.T.Road Scheme XM,
Beliaghata, Kolkata-700010.
West Bengal, India
Tel : (+91)(-33)2353-7470 extn.3203
(033)2363-3851;
E-Mail: dasss.niced@gov.in; santasabujdas@yahoo.com

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* Correspondence Author

Abstract

In late December 2019, an outbreak of novel coronavirus SARS-CoV-2 originated in Wuhan city of china, has infected over 30,00,000 people worldwide. SARS-CoV-2 is a causative agent of COVID-19 that has killed over 2,11,000 people and created social and financial crisis globally. Currently, there is no effective antiviral drugs and vaccine available for the prevention of COVID-19. Therefore, the scientific community is more focused on drug repurposing for the treatment of COVID-19. Here, we propose a network biology approach to identify candidate biomarkers for COVID-19. We critically analyze SARS-CoV-2 targeted human proteins and their interaction network. We utilize a combination of essential network centrality measures and

functional properties of human proteins to find the critical human targets for SARS-CoV-2 infection. From the candidate pool of 301 human proteins, interestingly we found that PRKACA, RHOA, CDK5RAP2, and CEP250 are candidates for therapeutic targets for COVID-19. PRKACA and CEP250 have also been found by another group for potential candidates for drug targets in treating COVID-19. We found that potential candidate drugs/compounds such as guanosine triphosphate, remdesivir, adenosine monophosphate, MgATP, and H-89 dihydrochloride for COVID-19. Most of the therapeutics development studies for COVID-19 are tried to block RNA synthesis through RNA dependent RNA Polymerase (RdRP). Our findings also suggest for blocking RNA synthesis in treating COVID-19.

Keywords: COVID-19, novel coronavirus, 2019-nCoV, SARS-CoV-2, drug repurposing, RdRP, network biology, rank aggregation, functional annotation.

1 Introduction

Coronavirus disease-2019 (COVID-19) is an ongoing pandemic resulting in 2,11,000 confirmed deaths among 30,00,000 confirmed cases in over 200 countries, area of territories as on 30th April 2020 (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>). The outbreak started in Wuhan city of china and rapidly spread all over the World [1]. COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is also called the 2019 Novel Coronavirus (2019-nCoV). In the last two decades, two highly pathogenic human coronaviruses including SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) have emerged [2]. In 2002 and 2003 SARS-CoV had led to 774 deaths among 8098 cases and MERS-CoV caused 858 deaths among 2494 confirmed cases in 2012 [3]. These three pathogens primarily target respiratory systems of the human. SARS-CoV-2 is appearing to be more

devastating compared to SARS-CoV and MERS-CoV [4]. Most of the patients of COVID-19 are asymptomatic or mild symptomatic but for few cases (mostly for older people and patients with pre-existing comorbidities) it may lead to deadly complications such as Acute Respiratory Distress Syndrome (ARDS), pneumonia, and multi-organ dysfunction. The common symptoms for COVID-19 are fever, dry cough, and tiredness; some patients may experience a runny nose, breathlessness, aches and pains, sore throat, and diarrhoea [5]. The virus spread has occurred by close contact between humans through droplets [6].

SARS-CoV-2 belongs to the family of single-stranded positive-sense RNA viruses [7]. The whole-genome sequencing reveals that SARS-CoV shares the highest sequence identity with SARS-CoV-2 (79.6%) [8]. Due to the unavailability of vaccine or antiviral drugs for COVID-19, it is extremely critical to manage a large number of patients. Quarantine, constant hand washing and social distancing are shown to be the most effective tactics for the control of the disease. However, scientists are putting their hard effort into the development of a vaccine for COVID-19. An article on 9th April 2020 reported that 73 vaccine candidates are at experimental or preclinical stages [9]. According to the latest news, the COVID-19 vaccine developed at the University of Oxford has been under human trial from 23rd April 2020. The University of Oxford group is hopeful that the vaccine will be available by September 2020 (<https://www.livemint.com/news/world/oxford-varsity-covid-19-vaccine-human-trials-from-thursday-uk-health-secretary-11587492981317.html>). For this current situation, the scientific community is focusing on drug repurposing to tackle the COVID-19 infection [7,8,10-12]. According to Wikipedia, drugs such as chloroquine, favipiravir, remdesivir, azithromycin, and lopinavir/ritonavir have been used for COVID-19. However, the efficacies of these above drugs are still controversial to the scientific community. For example, favipiravir is less effective in

severe COVID-19 patients. It is also not safe for pregnant women. The scientific community is not in favor of repurposing those drugs (lopinavir/ritonavir) that are particularly developed for HIV/AIDS [13]. Among these chloroquine/ hydroxychloroquine have been extensively reported and tested for COVID-19 treatment. However, there is still controversy that exists in the efficacy of chloroquine/ hydroxychloroquine for the treatment of COVID-19. An article currently in review at the New England Journal of Medicine suggested the administration of hydroxychloroquine to the hospitalized patient with COVID-19 did not appear to be beneficial for clinical outcomes such as mortality, risk for intubation, neutrophil-to-lymphocyte ratio and lymphopenia reconstitution [14]. A clinical trial conducted in Brazil was stopped when several patients with COVID-19 developed irregular heart rates, resulting in eleven deaths due to the administration of high doses of chloroquine. Therefore, there is still a scope for identifying drugs for repurposing. In addition to these, researchers are facing a continuous challenge to understand the novel coronavirus. Like other viruses, novel coronavirus also utilizes host machinery to complete its life-cycle within the host. Therefore, identification of critical host proteins might help the repurposing of host-dependent drug/compound for COVID-19.

For drug repurposing, few network biology studies have been introduced recently to identify critical host proteins and their interactor drug/compound [8,15,16]. However, their finding of key protein sets is not overlapping. Therefore, in this study, we have attempted to identify critical host targets for COVID-19 using a network biology study. Gordon *et al.* identified 67 druggable human proteins from 332 high confidence SARS-CoV-2-human protein-protein interactions (PPIs) [15]. We have utilized these 332 SARS-CoV-2-human PPIs for the identification of crucial host proteins for SARS-CoV-2. For this study, we consider important network biology and functional annotation properties of SARS-CoV-2 targeted human proteins.

Drug-protein interactions are also integrated into this study for the identification of candidate drug repurposing.

2 Methods

2.1 Collection of SARS-CoV-2-human Protein-Protein Interactions

We have obtained SARS-CoV-2-human protein-protein interactions (PPIs) from a recently published literature [15]. They have identified 332 SARS-CoV-2-human PPIs with high confidence using affinity purification-mass spectrometry (AP-MS). We have found 26 and 332 proteins for SARS-CoV-2 and human respectively, from the above 332 PPIs. It is observed that all the human proteins are reviewed and well-annotated proteins in UniProtKB [17]. We then sought for human PPIs for these 332 human proteins in the STRING database version 11 [18]. We have found 966 human PPIs among 301 human proteins with the combined scores > 0.4 . For further analysis, we have considered the above 966 human PPIs.

2.2 Network Properties

We have formed a network of 966 human PPIs using Cytoscape version 3.7.2 [19]. In this protein-protein interaction network (PPIN), each node indicates a protein and an edge indicates an interaction between proteins. We have integrated combined interaction score between proteins as an edge weight. Afterward, we have calculated decisive network properties including degree centrality (DC), closeness centrality (CC), betweenness centrality (BC) and eigenvector centrality (EC) of this edge-weighted network using CytoNCA [20]. CytoNCA computed these centrality measures for an edge-weighted network using the following equations.

$$\text{Degree Centrality (with weight)} : C_{D_w}(u) = \sum_{v \in N_u} w(u, v), \dots \dots \dots (1)$$

where, N_u is the node set containing all the neighbors of node u . $w(u, v)$ is the weight of the edge connecting node u and node v .

$$\text{Closeness Centrality (with weight)} : C_{C_w}(u) = \frac{|N_u| - 1}{\sum_{v \in V} \text{dist}_w(u, v)}, \dots \dots \dots (2)$$

where, $\text{dist}_w(u, v) = \sum_{(s,t) \in p} \text{cost}(s, t)$ is the weighted distance of the shortest path from node u to node v .

$$\text{cost}(s, t) = \frac{1}{w_{(s,t)}} \times (w_{(s,t)} > 0), w_{(s,t)} \text{ is the weight of the edge from node } s \text{ to node } t.$$

$$\text{Betweenness Centrality (with weight)} : C_{B_w}(u) = \sum_{s \neq u \neq t} \frac{p(s, u, t)}{p(s, t)}, \dots \dots \dots (3)$$

where, $p(s, t)$ is the total number of shortest paths from node s to node t .
 $p(s, u, t)$ is the number of those paths that pass through u .

$$\text{Eigenvector Centrality (with weight)} : C_E(u) = \alpha_{\max}(u), \dots \dots \dots (4)$$

where, $\alpha_{\max}(u)$ is the eigenvector corresponding to the largest eigenvalue of the weighted adjacency matrix A_w .

2.3 Rank Aggregation

We have calculated four different rankings of the human proteins in the above network using DC, CC, BC and EC values. Using excel formula we computed the median ranking score of each protein instead of exploring each ranking score individually. Subsequently, we sorted each human protein in the network using the median ranking score. Top 20 from the candidate pool of 332 human proteins have been considered for further analysis.

2.4 Functional Similarity

All possible combination pairs of the top 20 proteins were considered for functional similarity.

We employed the GOSim R package (version 1.22.0) to compute functional similarity for

protein pairs [21]. The Resnik terms similarity was calculated for all the three domains of gene ontology (GO), viz., molecular function (MF), cellular component (CC) and biological process (BP) [22].

2.5 Identification of Important Proteins

Eigenvector and eccentricity centrality are the significant centrality measures for identifying the influential nodes in a network [23]. In EC calculation, the weighted value of the link of a node is more important than the number of links. The GO similarity score of a protein pair is represented as an edge weight in the network. In an edge-weighted network, EC of each node was calculated using CytoNCA. Top 20 proteins of three cases (MF, CC, BP) were sorted using EC scores. To find the most influential proteins common in three cases, we considered the top 10 proteins from each case.

2.6 Enrichment Analysis of Pathway and GO

Identification of critical disease-associated pathways might help in the development of drugs. Pathway analysis helps explore the mechanisms of disease. The GO BP analysis assists to understand which processes need the support of a protein to complete. We used “Enrichr: a comprehensive gene set enrichment analysis web server” for the enrichment analysis of pathway and GO [24]. The Pathway with Adjusted P-value < 0.05 was considered as an enriched pathway. For GO BP enrichment analysis also we considered Adjusted P-value < 0.05 .

2.7 Drug-protein Interaction Network

To know the drug/compound target proteins, we also sought drug-protein interaction in STITCH database [25]. We examined only experimentally validated and manually curated databases to

find reliable drug-protein interactions. The drug/compound was prioritized using a combined score > 0.9 .

3 Results

We have found a candidate pool of 301 human proteins from 966 human PPIs (Figure1). The proteins are ranked based on their DC, CC, BC, EC scores. For DC, CC, BC and EC, we observed maximum rank 301, 300, 234 and 296 respectively (Supplementary Table 1). All the centrality measures are important for finding the crucial node in a network. Therefore, we sorted this list using median ranking scores and found a minimum score of 3.5 and a maximum score of 291 (Supplementary Table 2). Top 20 genes from this candidate pool of genes were extracted for functional similarity analysis (Table 1).

To know how the proteins function at the molecular level, the location of their function in the cell and the biological processes they support to complete, we included all the aspects of GO annotation. All the GO domains, viz., MF, CC and BP were considered. For a protein pair, all possible term similarities were calculated. We observed a minimum score of 0, a maximum score of 1 and mean of 0.317 for MF terms similarity score (Supplementary Table 3). For CC terms similarity score, we found the minimum and maximum scores of 0.158 and 1, respectively, while the mean was 0.632 (Supplementary Table 4). The mean of 0.547 was found for BP terms similarity score, with the minimum and maximum scores of 0 and 1, respectively (Supplementary Table 5).

Figure 1. Human PPIs of SARS-CoV-2 targeted human proteins, visualized by Cytoscape 3.7.2. The human proteins are represented by the nodes. The size and color of the nodes are different according to their degrees.

Table 1. Top 20 proteins based on the median ranking scores

Protein	DC_Rank	CC_Rank	BC_Rank	EC_Rank	Median_Rank
AKAP9	1	6	18	1	3.5
PRKACA	3	1	8	4	3.5
PRKAR2B	4	4	59	2	4
RAB1A	7	2	4	17	5.5
RAB8A	2	5	26	9	7
PCNT	5	10	43	3	7.5
CDK5RAP2	8	7	47	5	7.5
RAB7A	9	8	6	21	8.5
RHOA	13	3	5	16	9
CEP135	17	15	103	6	16
CNTRL	19	17	132	7	18
DDX10	6	30	7	105	18.5
PRKAR2A	26	13	104	13	19.5
RPL36	10	19	22	113	20.5

TUBGCP3	20	25	46	11	22.5
CEP250	21	24	234	8	22.5
RAE1	16	23	25	81	24
NUTF2	23	26	1	59	24.5
TUBGCP2	22	31	93	12	26.5
OS9	35	18	2	133	26.5

We constructed three networks using different GO similarity scores. For a protein pair, the GO similarity score was treated as the weight of an edge among them. For these networks, only the edge weights (GO similarity scores) were different, while nodes and number of edges, as well as their connections, were the same. For eigenvector centrality calculation, only the edge weights were the main differentiator for these networks. As shown in Table 2, the eigenvector centrality score for MF, CC, and BP ranged between 3.86E-13 to 0.33, 0.09 to 0.28 and 0.11 to 0.27, respectively (Figure 2 and Supplementary Figure S1 and S2).

Table 2. Eigenvector centrality score of human protein using GO MF, CC and BP similarity score

Protein	Eigenvector centrality score		
	MF	CC	BP
AKAP9	0.221214	0.183526	0.247266
CDK5RAP2	0.278605	0.272746	0.256644
CEP135	0.107631	0.198114	0.23159
CEP250	0.203105	0.273835	0.241416
CNTRL	0.118379	0.204541	0.234498
DDX10	0.270821	0.265321	0.10762
NUTF2	0.14052	0.250276	0.162841
OS9	0.310271	0.095256	0.170248
PCNT	0.114475	0.17833	0.269729
PRKACA	0.326611	0.265322	0.240817

PRKAR2A	0.333194	0.262849	0.157465
PRKAR2B	0.333194	0.265352	0.212394
RAB1A	0.307002	0.249588	0.22605
RAB7A	3.86E-13	0.243784	0.233122
RAB8A	2.71E-11	0.279244	0.248546
RAE1	0.199742	0.135516	0.200893
RHOA	0.317055	0.247685	0.244188
RPL36	0.037185	0.132995	0.252692
TUBGCP2	0.140298	0.164321	0.229425
TUBGCP3	0.140298	0.167172	0.233789

Figure 2: Distribution of eigenvector centrality measure scores for GO MF.

In each case, 10 proteins with the highest eigenvector centrality score were considered to find the most common influential protein set. Interestingly, we found 4 proteins (gene name PRKACA, RHOA, CDK5RAP2 and CEP250) were common to all the three cases (Figure 3). The pathway enrichment analysis of the 4 proteins showed pathways, such as vascular smooth muscle contraction, chemokine signaling pathway and viral carcinogenesis etc. (Supplementary Table 6). The gene ontology biological process enrichment analysis showed enriched biological

processes like ciliary basal body-plasma membrane docking, cell cycle G2/M phase transition, mitotic cell cycle phase transition and cilium assembly (Supplementary Table 7).

Figure 3. Venn diagram of eigenvector centrality based top 10 proteins from each GO similarity scores (MF, CC, BP).

The drug-protein interaction network analysis of the above 4 proteins has shown interaction with drug/compound (Table 3). PRKACA interacts with H-89 dihydrochloride, balanol, MgATP (magnesium ATP), MgADP (magnesium ADP), magnesium, manganese and adenosine monophosphate, etc. (Figure 4). RHOA interacts with phosphate, magnesium (Supplementary Figure S3). Both CDK5RAP2 and CEP250 interact with MgATP, MgADP and guanosine triphosphate (Supplementary Figure S4-S5).

Table 3. Identified drugs/compounds that modulate SARS-CoV-2 interactor

Protein	Drug/ Compound	Experimentally_ determined_ interaction	Database_ annotated	Combined_ score	PubChem CID
PRKACA	pSer	0.957	0.8	0.991	24779545
PRKACA	A-674563	0.942	0.8	0.988	11314340
PRKACA	H-89	0.91	0.8	0.981	5702541

	dihydroch.				
PRKACA	balanol	0.911	0.8	0.981	5287736
PRKACA	A-443654	0.912	0.8	0.981	10172943
PRKACA	calcium ions	0.795	0.9	0.978	271
PRKACA	MgATP	0.795	0.9	0.978	15126
PRKACA	magnesium	0.795	0.9	0.978	5462224
PRKACA	MgADP	0.795	0.9	0.978	30103
PRKACA	manganese	0.795	0.9	0.978	15551713
PRKACA	adenosine mono.	0.795	0.9	0.978	6083
PRKACA	phosphate	0.795	0.9	0.978	1061
RHOA	phosphate	0.933	0.9	0.993	1061
RHOA	magnesium	0.852	0.9	0.984	5462224
CDK5RAP2	MgADP	0	0.9	0.9	30103
CDK5RAP2	MgATP	0	0.9	0.9	15126
CDK5RAP2	guanosine trip.	0	0.9	0.9	135398633
CEP250	guanosine trip.	0	0.9	0.9	135398633
CEP250	MgATP	0	0.9	0.9	15126
CEP250	MgADP	0	0.9	0.9	30103

Figure 4. PRKACA protein interactions in STITCH database.

4 Discussion

To understand disease progression, diagnosis and treatments, the SARS-CoV-2 targeted human proteins and their interaction network is crucial. Identification of critical human targets for SARS-CoV-2 infection might help the development of an effective treatment. We proposed a novel network biology approach to identify critical human targets for SARS-CoV-2 infection, using SARS-CoV-2-human and human PPIs. The concept of centrality measures such as DC, CC, BC, and EC have been used extensively to identify important proteins in PPIN [26-28]. The majority of network analysis methods have utilized only one or two centrality measures at a time for the identification of important proteins from PPIN. However, it is still not clear that which centrality measure is the best among them. Therefore, here we considered all the above centrality measures to identify important human proteins. We computed four different ranks for each protein using DC, CC, BC and EC scores. To find the key protein set for SARS-CoV-2 infection, we opted for a median ranking score instead of considering each ranking method individually. The top 20 proteins from the candidate pool of 301 proteins were considered for the identification of the most crucial protein set for SARS-CoV-2 infection.

The average term similarity scores of 0.317, 0.632, and 0.547 were found for MF, CC, and BP, respectively. Hence, notable functional similarities were found among the top 20 genes. To find the most prominent protein from the top 20, we have computed eigenvector centrality for these proteins using MF, CC, and BP terms similarity score. We found PRKACA (UniprotID: P17612), RHOA (UniprotID: P61586), CDK5RAP2 (UniprotID: Q96SN8), and CEP250 (UniprotID: Q9BV73) human proteins with high eigenvector centrality were common to all three cases. Therefore, we considered these 4 human proteins as the most influential for SARS-CoV-2 infection. The pathways and GO BP enrichment analysis of these 4 proteins showed critical pathways and biological processes for infections.

Among the 4 proteins, PRKACA and CEP250 have recently been reported as potential drug candidates by the expert group of Gordon *et al.* [15]. They found that PRKACA and

CEP250 proteins are interacting with nonstructural protein -13 (Nsp13) of SARS-CoV-2. During SARS-CoV-2 infections, host interactions of Nsp13 (golgins) may enable the dramatic reconfigurations of Golgi trafficking. The expert group also suggested compounds for targeting PRKACA and CEP250 as H-89 and WDB002, respectively. We also found that compound H-89 for PRKACA. For cardiovascular diseases (CVD), PRKACA protein plays an important role [29]. The patients with CVD are more prone to develop COVID-19 and high-risk of developing severe disease with poorer clinical outcomes [30,31]. Therefore, PRKACA protein has good merit for investigation as a drug target of COVID-19. RHOA protein is a known target for cancer and a potential target for diabetes [32-34]. Patients with pre-existing cancer and diabetes are more vulnerable to develop severe COVID-19 [31,35]. Therefore, RHOA might be a potential candidate for the drug target of COVID-19.

The drug-protein interactions analysis of these 4 proteins exhibits the most common interactions with MgATP, MgADP, magnesium, and guanosine triphosphate drug/compound. A recent article proposed that the supervision of guanosine triphosphate might cause reduction of cellular magnesium level via conversion to MgATP (magnesium ATP). Therefore, the reduction of magnesium level results in blocking RNA synthesis through RNA dependent RNA Polymerase (RdRP). The authors suggested that blocking RNA synthesis in treating COVID-19 [36]. Alternatively, it is observed that remdesivir among the drugs have been repurposing for COVID-19, binds to RdRP, and terminate RNA-chain [13,37,38]. The mechanism of action of remdesivir is similar to our key finding [39]. Therefore, remdesivir drug might be utilized for treating COVID-19.

5 Conclusion

SARS-CoV-2 abuses the host machinery, mainly the host PPIs for infection. SARS-CoV-2 targeted human proteins and their intra-species interactions are therefore important to understand the mechanism behind the infection. The identification of critical human proteins for COVID-19 is crucial for the development of host-directed drugs. We found a more influential human protein set for COVID-19 by integrating SARS-CoV-2-human PPIs and interaction dynamics of human PPIs. Our finding suggests that 4 out of 301 proteins have a meaningful role in SARS-CoV-2

infection. Thus, the above proteins may be potential biomarkers for SARS-CoV-2 infection. Two out of four proteins were also reported by another study as the potential drug candidates. Another two proteins have good merit for investigating as potential drug candidates. The study also prioritized candidate repurposing drugs for COVID-19. Further experimental and clinical validations are required to substantiate the findings in this article.

Availability of Data

Supplementary information is available at

<https://github.com/ranjan1010/COVID-19WorkByBarmanEtal2020>

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Authors' contributions

R.K.B., A.M., U.M. and S.D. conceived and designed experiments, R.K.B. executed experiments, R.K.B., A.M., U.M. and S.D. analyzed data and wrote manuscript.

Competing interests

The authors declare that they have no competing interests.

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