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Exploring SARS-CoV2 host-pathogen interactions and associated fungal infections cross-talk: Screening of targets and understanding pathogenesis

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ABSTRACT

The COVID-19 associated opportunistic fungal infections have posed major challenges in recent times. Global scientific efforts have identified several SARS-CoV2 host-pathogen interactions in a very short time span. However, information about the molecular basis of COVID-19 associated opportunistic fungal infections is not readily available. Previous studies have identified a number of host targets involved in these opportunistic fungal infections showing association with COVID-19 patients. We screened host targets involved in COVID-19-associated opportunistic fungal infections, in addition to host-pathogen interaction data of SARS-CoV2 from well-known and widely used biological databases. Venn diagram was prepared to screen common host targets involved in studied COVID-19-associated fungal infections. Moreover, an interaction network of studied disease targets was prepared with STRING to identify important targets on the basis of network biological parameters. The host-pathogen interaction (HPI) map of SARS-CoV2 was also prepared and screened to identify interactions of the virus with targets involved in studied fungal infections. Pathway enrichment analysis of host targets involved in studied opportunistic fungal infections and the subset of those involved in SARS-CoV2 HPI were performed separately. This data-based analysis screened six common targets involved in all studied fungal infections, among which CARD9 and CYP51A1 were involved in host-pathogen interactions with SARS-CoV2. Moreover, several signaling pathways such as integrin signaling were screened, which were associated with disease targets involved in SARS-CoV2 HPI. The results of this study indicate several host targets deserving detailed investigation to develop strategies for the management of SARS-CoV2-associated fungal infections.

1. Introduction

A large number of COVID-19 patients face several health issues even after recovery. Among these, complications caused by secondary infections pose major challenges for researchers and healthcare workers. Fungal infections constitute considerable proportion of such secondary infectious complications [28,64]. These fungal infections contributed to a significant number of post-COVID-19 mortality even after recovery from SARS-CoV2 infections [17]. Various fungal infections were reported with COVID-19 patients, including candidiasis [24,32,47], mucormycosis [49,21], aspergillosis [2,6,10,39,51,63,73,75,78,60], cryptococcosis [3,22], and *Pneumocystis* pneumonia [50,30] etc.

Although investigations are ongoing and yet to generate complete understanding, COVID associated immunosuppression, hypoxia, hyperglycemia, host iron depletion in addition to prolonged hospitalization, use of corticosteroids, and mechanical ventilation have been hypothesized to increase the risk of occurrence of fungal infections among patients experiencing COVID-19 disease [5]. Moreover, efforts by the global scientific community are unravelling the molecular mechanisms of SARS-CoV2 pathogenesis at a rapid pace. Coordinated efforts have identified several host-pathogen interactions (HPI) of SARS-CoV2 in a very short time span [23]. In addition, recent system biological approaches have made it feasible to study complex, multiple host-pathogen interactions in

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meaningful ways [35]. On the other hand, information about host targets involved in different diseases are also getting generated through several discrete investigations. Although COVID-19-associated fungal infections were not at the center of discussion for researchers prior to the pandemic, several studies have identified different host targets involved in such infections. A number of databases have catalogued these disease targets and made it feasible to study complex multi-disease pathogenesis using system biological approaches.

During the present study, host targets involved in COVID-19-associated fungal infections were screened in addition to the identification of common targets involved in studied fungal infections. Moreover, the HPI data of SARS-CoV2 was used to screen its potential to influence these important fungal disease targets. This database approach was utilized to screen host targets involved in COVID-19-associated fungal infections and to screen important targets which might inform further laboratory studies and clinical investigations for development of appropriate intervention.

2. Material and methods

2.1. Database

The host targets involved in different COVID-19-associated opportunistic fungal infections were screened from DisGeNet and GeneCards. The disease targets involved in invasive aspergillosis, mucormycosis, invasive candidiasis, *Cryptococcus neoformans* infection, and *Pneumocystis jirovecii* pneumonia, were screened from both databases. The targets thus obtained from both databases were combined and redundant targets obtained from multiple databases were removed and unique targets involved with a particular infection were used for further analyses. In addition, SARS-CoV2 HPI data was obtained from the biological interaction database BIOGRID.

2.2. Identification of common targets

The human targets involved in all studied opportunistic fungal infections were screened further for their involvement in single or multiple opportunistic fungal infections. A Venn diagram was constructed to identify the disease targets commonly involved in multiple opportunistic infections associated with SARS-CoV2 infections.

2.3. Construction of disease targets interaction network

The interaction network of disease targets was prepared through the interaction database STRING [81]. Cytoscape V 3.8.0 was used to visualize interactions. Common interactions were also identified in the interaction network and network biological parameters were predicted through network analyzer. Python package mygene 3.2.2 along with DAVID bioinformatics resources 6.8 [79] were used to map gene symbols.

2.4. Construction of SARS-CoV2 host-pathogen interaction network and identification of disease targets

The interaction data obtained from BIOGRID was used to construct a network of SARS-CoV2 HPI. BIOGRID v 4.4 was used to download all SARS-CoV2 and coronavirus-related interactions (Last modified till 30th Nov 2021). SARS-CoV2 interactions with human were filtered out and were used further. This interaction network was superimposed on host fungal disease target networks constructed in an earlier step in order to predict the potential of SARS-CoV2 in modulating fungal disease targets.

2.5. Functional enrichment analysis of disease targets

Functional enrichment analysis of disease targets involved in COVID-19 associated fungal infections and the subset of these targets involved in SARS-CoV2 HPI were separately analyzed for functional enrichment analysis. PANTHER Over-representation test (Released 20210224) with annotated version 16.0 and release date 2020-12-01 was used to analyze over-represented pathway associated with each gene target set using annotation data set PANTHER pathways. Fisher's Exact test with statistical correction using False Discovery Rate (FDR) was used to screen over-represented pathways associated with target sets [80].

3. Results

3.1. Screening of targets

The details of screened human targets involved in different opportunistic fungal infections are presented in Table 1. The disease targets commonly involved in different studied opportunistic infections associated with COVID-19 are presented in Supplementary Table S1. The numbers of disease targets commonly involved in different studied fungal infections are presented in Fig. 1 as a Venn diagram. The roles of common targets in fungal infections and COVID-19 are presented in Table 2.

3.2. Construction of disease target interaction network

The disease targets interaction network screened 30,280 interactions among targets using STRING with a default threshold confidence (score) cutoff 0.4. Such interactions were further screened for their involvement in COVID-19-associated opportunistic fungal infections. Fig. 2 indicates targets interaction network and their importance in studied infections on the basis of degree value.

3.3. Host-pathogen interaction analysis of SARS-CoV2

BIOGRID v4.4 COVID 19 coronavirus project interactions file found a total of 25,983 interactions between SARS-CoV2 and *H. sapiens* after the removal of HPI involving other organisms. These HPIs found 18,730 unique SARS-CoV2 and *H. sapiens* HPIs stored in BIOGRID available version involving 30 SARS-CoV2 and 5110 *H. sapiens* targets.

3.4. Screening of SARS-CoV2 interaction with targets involved in studied fungal infections

During the screening, a total of 357 out of 5110 SARS-CoV2 HPI human targets were found to be involved in studied fungal infections. These 357 targets were involved in unique 1445/2110 SARS-CoV2 HPI screened from BIOGRID v4.4. The details of these HPIs are shown in Table S2 while the HPI network of these targets

Table 1
Screening of human targets involved in studied COVID-19 associated opportunistic fungal infections from disease target databases.

Infection	Targets from DisGeNet	Targets from Genecard
Invasive aspergillosis	59	239
Cryptococcus neoformans infection	167	181
Pneumocystis carinii pneumonia	180	141
Mucromycosis	9	20‘
Candidiasis	73	669

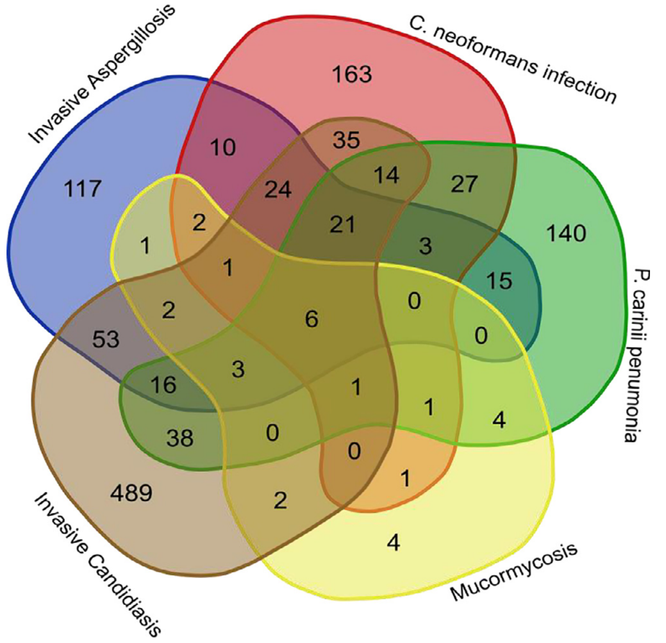

Fig. 1. Venn diagram of screened disease targets involved in COVID-19 associated studied opportunistic fungal infections.

is presented in Fig. 4. All the studied COVID-19-associated fungal infection disease targets with high degree value, shown in Fig. 2, were not directly interacting with SARS-CoV2 as per HPI data. The details of SARS-CoV2 interacting targets among the top 20 high-degree value nodes irrespective of their involvement in number of studied fungal infections are presented in Table 3 with their role in fungal infections and COVID-19.

3.5. Functional over-representation analysis of targets involved in studied fungal infections

The result of PANTHER pathway over-representation analysis is presented in Fig. 5; results are arranged as per their FDR value.

4. Discussion

While efforts were deployed to manage the COVID-19 pandemic through identification of suitable preventive and therapeutic means, opportunistic fungal infections posed additional challenges for the scientific community and gained wide media attention. Several opportunistic fungal infections appeared among COVID-19 patients. For example, the estimated occurrence of invasive pulmonary aspergillosis among COVID-19 patients ranged from 19.6 to 33.3 % [43]. Similarly, cases of mucormycosis also surged among COVID-19 patients, especially during the second wave of the pandemic in certain geographic locations [26]. Moreover, the cases of candidiasis, pneumocystosis, and cryptococcosis were also reported as emergent fungal infections among COVID-19 patients in addition to aspergillosis and mucormycosis [9]. Several species of fungi belonging to different genera of commonly occurring opportunistic fungal infections were reported to contribute to these opportunistic infections among COVID-19 patients. We therefore screened host targets involved in such infections, in order to understand the involvement of host in the pathogenesis of these infections.

On the other hand, several novel characteristics of SARS-CoV2 presented additional challenges to the scientific community. Fortu-

Table 2
Common host target screened to be involved in all studied COVID-19 associated opportunistic infections, their role and interactions with SARS-CoV2.

Common Host targets	Role in opportunistic fungal infection	Role in SARS-CoV2	Screened Interaction with SARS-CoV2
Caspase recruitment domain-containing protein 9 (CARD9)	It plays a key role in innate immunity against fungi through the formation of signaling complexes [4].	The publication reporting this interaction indicates that HPI of SARS-CoV2 are enriched with proteins involved in inflammation, immune signaling, ubiquitination, and membrane trafficking and also suggests that these binary interactions can be prioritized as therapeutic targets [36]	nsp16
C—C chemokine receptor type 6 (CCR6)	CCR6 plays an important role in leukocyte recruitment during pathogen exposure. It binds to CCL20 and acts as an important contributor of lung and gut immunity [29]. It is also found that CCR6-mediated dendritic cell influx acts as a starting defense mechanism against fungal infection [56].	It is found that CD8 + T cells from COVID-19 patients BALF are enriched with CCR6 +. It was suggested that this is due to the high CCL20 level in BALF of COVID-19 patients [65].	–
Interferon- gamma (IFNG)	It plays a key role in antimicrobial response and is produced by immune cells like *T*-cells and NK cells. It is proposed as adjunctive immunotherapy for invasive fungal infections [15].	The level of interferon-gamma is suggested as an important marker for deciding the fate of COVID-19 patients from survival to death and it was proposed that combined therapies targeting such cytokines may be beneficial for COVID-19 patients [19].	–
C-type lectin domain family 7 member A (CLEC7A)	Lectins function as pattern recognizing receptors for recognizing pathogenic bacteria and fungi and mediate TLR2 signaling and resultant inflammatory response. It is also known to promote the fungicidal activity of human neutrophils [34].	Other lectins are involved as a receptor for SARS-CoV2 [25]	–
Lanosterol 14-alpha demethylase (CYP51A1)	It is involved in sterol biosynthesis. Azoles inhibit its activity thereby this mechanism contributes to their antifungal activity [53].	SARS-CoV2 host interactions upregulate proteins involved in cholesterol metabolism, including CYP51A1 by nsp6. Cholesterol metabolism Is known to play an important role in SARS-CoV2 replication and it is also suggested as an important therapeutic target for SARS-CoV2 [61,69].	E, M, S, nsp2, nsp4, nsp6, ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF14
Granulocyte-macrophage colony-stimulating factor (CSF2)	Plays an important role in antifungal defense during respiratory fungal exposure through mediating neutrophil antifungal activity and oxidative burst [31].	GM-CSF is shown to be involved in both antiviral immunity and pro-inflammatory hypercytokinaemia during COVID-19. Therefore, its blockade and administration both are suggested as therapeutic strategies [48].	–

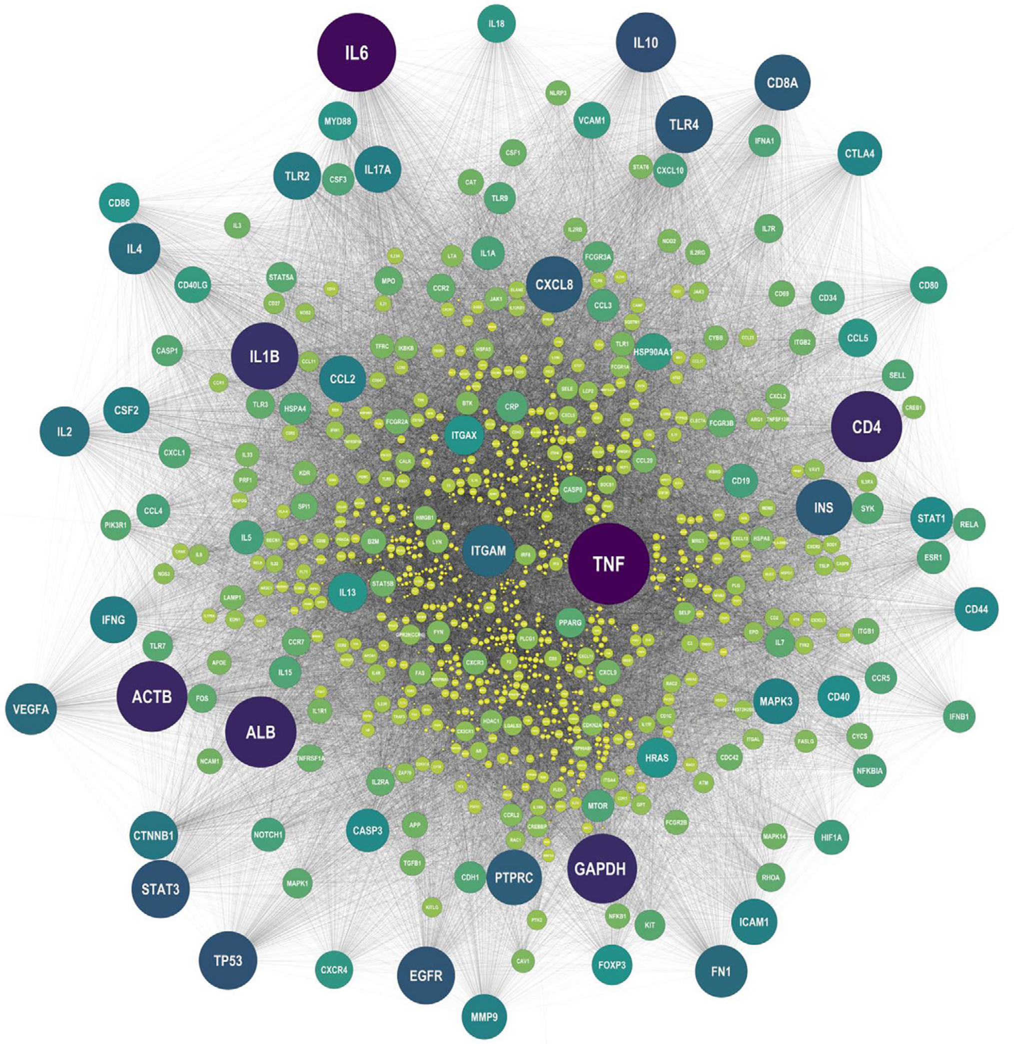

Fig. 2. STRING interaction network of host targets screened with studied COVID-19 associated opportunistic fungal infections. Target node sizes and colors are arranged as per their relative degree values, which represent their interactions and therefore their centrality in the presented network. Vide table S1 for greater details. Large/dark color and small/light color nodes indicate highest to lowest degree values of given targets.

nately, unprecedented global coordination unveiled several aspects of SARS-CoV2 pathogenesis within a very short time. Several recent studies have identified interactions of SARS-CoV2 with the host and their influence on pathogenesis. A number of open-access databases have collated these interactions and provided them for analysis. BIOGRID is one such biomedical interaction repository with its version 4.4.205 comprising 2,392,652 protein and genetic interactions and these numbers are continuously increasing. It has a separate COVID-19 coronavirus curation project providing coronavirus related HPI with literature backed evidence used during the study [52].

In contrast, comparatively less information is available about COVID-19-associated fungal infections. Still, the targets involved in these infections are identified and compiled in disease target databases such as DisGeNet and GeneCard, etc. [68,58]. Such databases compiling information about disease targets and molecular host-pathogen interactions have greatly revolutionized the understanding of molecular pathogenesis of diseases. In addition, the network biological methods coupled with visualization tools such as Cytoscape have made it feasible to infer meaningful information from such large, complex interaction datasets [66].

It is reported that COVID-19 may increase the chance of occurrence of several other fungal, bacterial and viral infections, especially during prolonged hospital stay [42]. These infections are associated with severe COVID-19 disease and poor outcomes [18]. The overlapping symptoms of COVID-19-associated fungal infections add to the difficulty in diagnosis [5] and management of patients. We maintain that such overlapping symptoms may have their roots in overlapping pathogenic mechanisms and thus disease targets and may hint at possible intervention strategies (Fig. 1) from the perspective of patient management. The screening of disease targets found several important findings during our analyses. Six host targets, including CARD9, CCR6, IFNG, CLEC7A, CYP51A1, and CSF2 were found common among all studied fungal disease targets (Table S1, Fig. 1). Among these targets, CARD9 and CYP51A1 were also found to be involved in host-pathogen interactions with SARS-CoV2. The biological implication of these targets in fungal infections and COVID-19 are presented in Table 2. It indicates that these targets are primarily involved in response to fungal infections, at the same time they are involved in immune signaling during SARS-CoV2 infections (Table 2). Screening of such dual-edge targets involved in both SARS-CoV2 and associated fungal infections could unravel their potential for serving as sites for therapeutic intervention.

Although the fungal disease target interaction analysis through STRING found that there are several important targets on the basis

Table 3
SARS-CoV2 interacting nodes with high degree value in fungal infections target network and their role in fungal infections and COVID-19.

Sr. No.	Human Target	Role in fungal infection	Role in COVID-19	Interaction with SARS-CoV2
1	Albumin (ALB)	Human albumin enhances the pathogenic potential of *Candida* by providing multiple benefits to fungi, such as increased iron access, growth, and adhesion [55]	Hypoalbuminemia is considered a risk factor for SARS-CoV2 patients and therefore albumin infusion is considered an important factor to improve outcomes [62].	E nsp11 nsp14 nsp15 nsp16 ORF7b S
2	Actin, cytoplasmic 1 (ACTB)	Fungal infection, such as *Candida* is already known to affect cellular actin during the study of interactions between *Candida* and HEp2 cells [70]. *Candida* is also known to stimulate actin polymerization by *C. albicans* phagosomes which help them to escape growing yeast from macrophages [27]	SARS-CoV2 interaction with the actin cytoskeleton and related functions is important for viral pathogenicity, infection and other necessary functions [38].	E nsp4 ORF10 ORF7b ORF8
3	Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)	It is identified as an important adhesion factor for fungal host interaction during the study of *Penicillium marneffei* [44]	GAPDH is suggested to play various roles in responses against SARS-CoV2 infection and therefore proposed as an inhibitor for coronaviruses through IFN gamma and NO pathways [8]	M E nsp13 nsp4 nsp6 ORF10 ORF8 S
4	Tumor suppressor p53 (TP53)	p53-like proteins from *C. albicans* are essential for virulence, hyphal growth, and antifungal resistance [33]. Some antifungal agents also induce p53 dependent apoptosis in cancer cells [14]	Coronavirus can induce cell cycle arrest through p53-dependent mechanisms and inflammatory cytokines also positively correlate with p53 [11]	E nsp4 nsp8 ORF10 ORF3b ORF7a ORF8 S
5	Epidermal growth factor receptor (EGFR)	EGFR signaling contributes to mucormycosis and inhibition of its signaling is proposed as an approach to management of mucormycosis [76]	GFR signaling is an important mechanism for the pathogenesis of SARS-CoV2 and its inhibition is suggested as an important target for the management of COVID-19 by inhibition of SARS-CoV2 replication [37]	S M nsp4 ORF3a ORF7b
6	Fibronectin (FN1)	Fibronectin plays an important role in the pathogenesis of *Candida* spp. by acting as an epithelial surface receptor [12,41]	SARS-CoV2 modulates extracellular matrix proteins expression, including fibronectin expression and it is suggested as a biomarker to track disease severity in COVID-19 patients [45]	nsp6
7	TLR4	TLR4 signaling my influence fungal infections by modulating pro-inflammatory immunity and regulatory T cells [46]	SARS-CoV2 binding to TLR4 is suggested to increase ACE2 expression and subsequent viral entry and hyperinflammation [1]	S

of degree value (Fig. 2), the SARS-CoV2 was also found to interact with several of these targets but not all (Fig. 4). The host-pathogen interaction network displayed in Fig. 3 indicates that SARS-Cov2 M, ORF7b, and nsp4 targets have maximum number of interactions as per available HPI data and these targets are involved in several interactions with host including opportunistic fungal infections targets.

Degree value is an important network biological parameter indicating the centrality of a node in a particular network and therefore Fig. 2 represents targets with the maximum number of interactions on the basis of different node sizes. Though TNF, IL6, ALB, CD4, ACTB, GAPDH, IL1B, IL10, TP53, STAT3, EGFR, TLR4, CXCL8, INS, CD8A, PTPRC, ITGAM, FN1, IL4, VEGFA were top 20 fungal disease targets according to degree value (Fig. 2), but SARS-CoV2 was screened to perform host-pathogen interactions with ALB, ACTB, GAPDH, TP53, EGFR and TLR4, FN1 among these top 20 targets (Fig. 4). The role of these targets in opportunistic fungal infections and COVID-19 indicated that they could play an important role in the etiology of this association (Table 3) and could merit independent future investigation. Similarly, among the targets commonly involved in all studied fungal infections, only CARD9 and CYP51A1 were screened with known HPI with SARS-CoV2 (Table 2, Fig. 4). The role of CARD9 signaling is already reported in protection against fungal infections [16]. Certain articles hypothesized the role of pioglitazone (thiazolidinedione) in modulating lung injury in COVID-19 patients, which is an inhibitor of the NF-kB and MAPK pathways by reducing expression of CARD9 [13,72]. Though it is reported that CARD9 plays a protective role in fungal infections, it is known to play an ambivalent role in viral diseases as in cases of influenza and coxsackievirus [54]. Therefore, this dual-edge sword needs experimental investigations to understand the role of CARD9 signaling in modulating fungal infection susceptibility among COVID-19 patients.

CYP51A1 encodes for cytochrome P450 superfamily of enzymes involved in drug metabolism and synthesis of several important molecules. Some infectious organisms also modulate the expression of CYP51A1 affecting disease pathogenesis [57]. Studies have identified the role of CYP51A1 in fungal diseases and their role is already established in antifungal drug resistance [74,77]. Frequent use of antifungal agents pose an additional challenge of development of drug-resistant pathogens mediated therapeutic failure and requires development of new antifungals, which is a difficult task [7]. Due to the important role of CYP51A1 in fungal infections and their screened interactions with SARS-CoV2, it requires a legitimate appraisal to understand its role in COVID-19-associated opportunistic fungal infections. Table 2 summarizes the biological potential of common fungal disease targets and their possible implications in SARS-CoV2 and fungal infections.

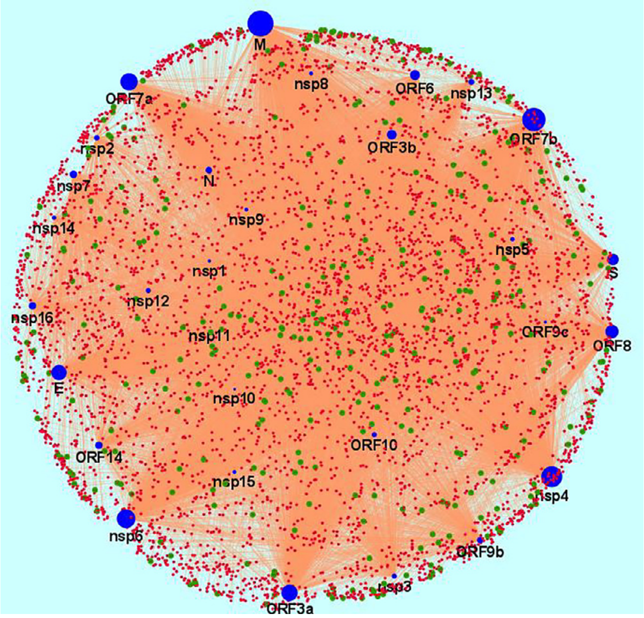

Fig. 3. Host-pathogen interaction network screened from BIOGRID. Viral targets are shown in blue color while human targets are shown in red color nodes. Sizes of the viral nodes are arranged as per their relative degree value, while the interaction of SARS-CoV2 with targets involved in COVID-19 associated studied opportunistic fungal infections are shown in green color. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Functional enrichment analysis of fungal disease targets and the subset of those involved in HPI with SARS-CoV2 reveals several important pathways indicating their importance in the development of SARS-CoV2-associated opportunistic fungal infections (Fig. 5). It is reported that integrin activation is important for SARS-CoV2 infection [67], and this pathway is enriched with studied disease targets. Integrins are involved in host-pathogen interactions with several fungi, bacteria and viruses, and their role in the pathogenesis of pulmonary pathogens is already reviewed in literature [71]. *Pneumocyctis carinii* induces integrins upregulation possibly leading to enhanced adherence of pathogen to lung cells [59]. Moreover, some fungi such as *Pneumocystis* and *Candida* possess integrin-like molecules that mediate fungal adhesion [20,40]. The common involvement of integrin signaling in pulmonary infections and their modulation by SARS-CoV2 and fungal pathogens also indicate several caveats about the role of this mechanism in COVID-19-associated opportunistic fungal infections.

This large data-based analysis screens pathways and targets that might be used to develop management strategies. Although the findings of this study screen and predict several targets and pathways involved in COVID-19-associated opportunistic fungal infections, the limitation of computational studies must be considered while making interpretations as with other experimental approaches. The study is based on existing databases compiling different disease targets and host-pathogen interactions from different investigations. As information in these databases are regularly updated, addition of more targets will lead to incremental accumulation of knowledge on the subject and would demand revisiting the current investigation findings. Finally, computational methods also have some limitations due to the background algorithm analyzing the result. Nevertheless, the experimental evaluation of large data involves huge economic and labor efforts. Therefore this study holds its value by screening several important targets and pathways. In conclusion, the current investigation has added value to the existing knowledge by identifying important

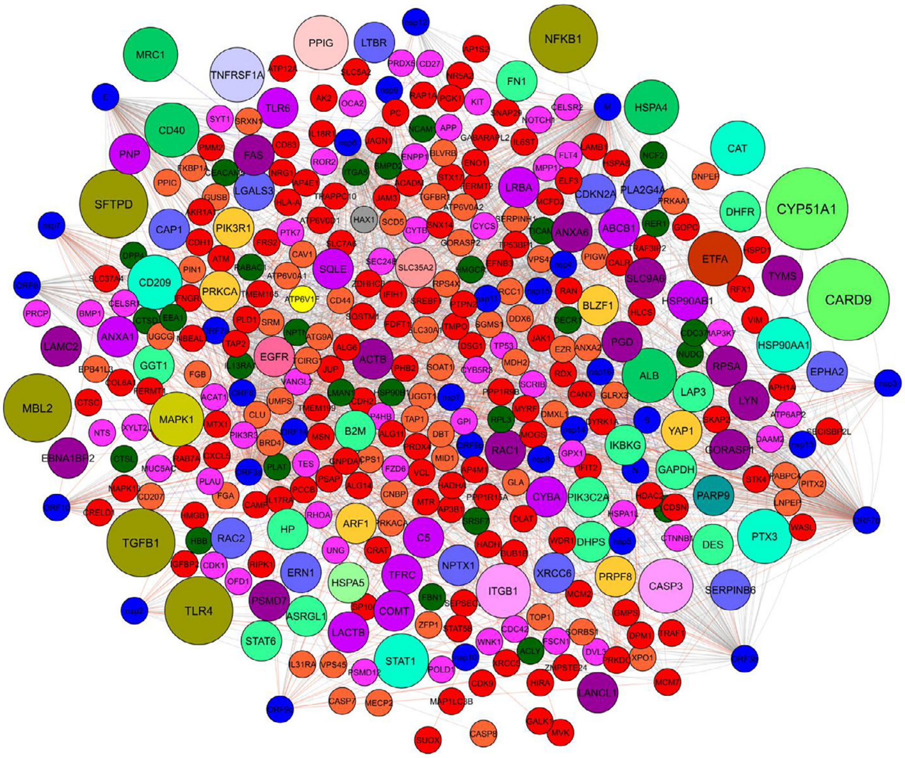

Fig. 4. Interactions of SARS-CoV2 with human targets involved in studied opportunistic fungal infections. Viral proteins are presented in blue color while human proteins are colored as per their involvement in different set of studied infections. Sizes of the human protein nodes are arranged as per their involvement in number of studied infections. For instance, CARD9 and CYP51A1 were screened as targets involved in all 5 studied infections and therefore presented as largest nodes in interaction network and so on. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

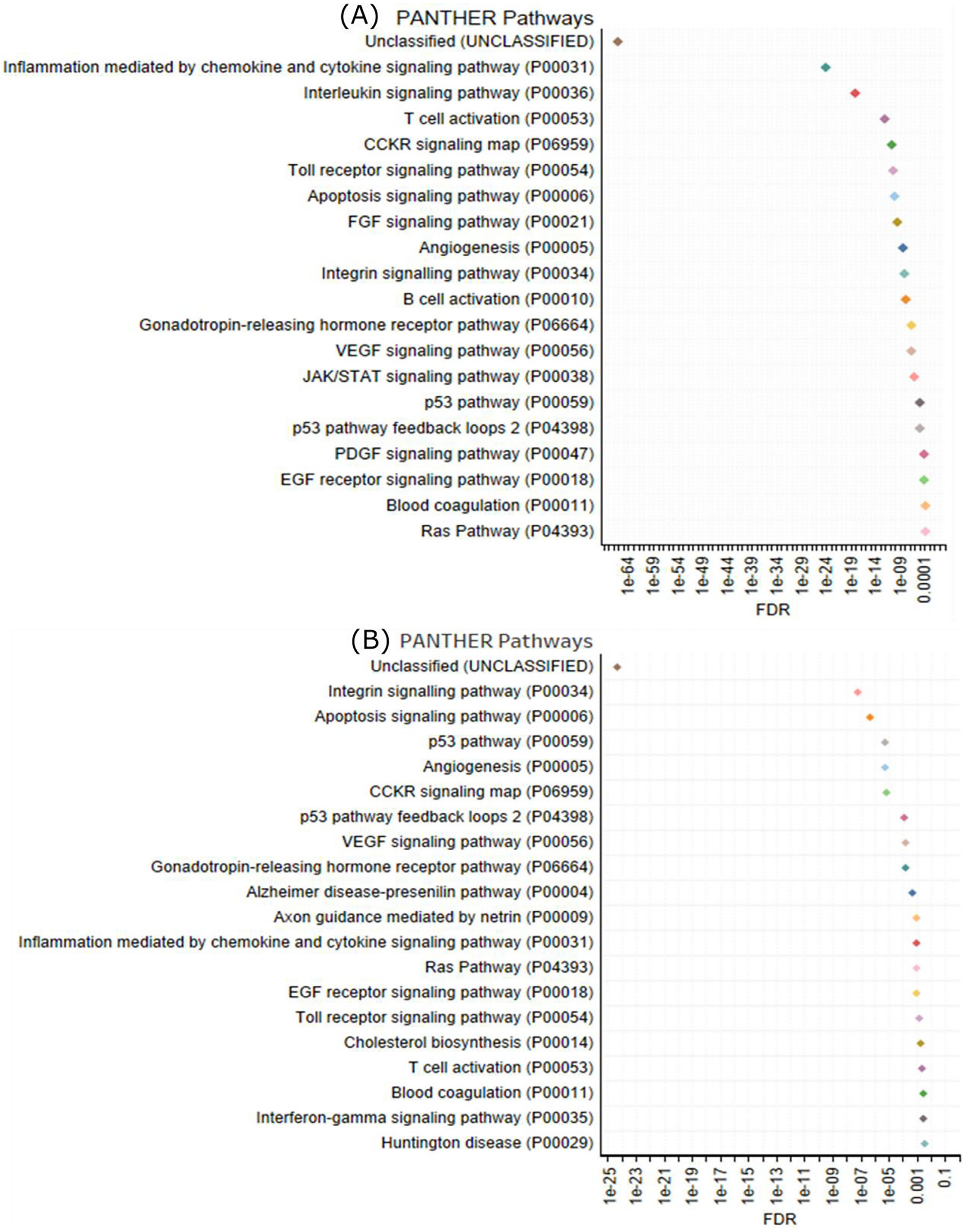

Fig. 5. Pathway over-representation analysis of disease targets involved in COVID-19 associated studied opportunistic fungal infections (A) and subset of these targets involved in SARS-CoV2 HPI (B) through PANTHER pathway over-representation test.

targets for management of COVID-19-associated opportunistic fungal infections.

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CRediT authorship contribution statement

Abdul Arif Khan: Conceptualization, Methodology, Writing – original draft. **Sudhir K. Jain:** Conceptualization, Writing – review & editing. **Mahendra Rai:** Conceptualization, Writing – review & editing. **Samiran Panda:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.csbj.2022.08.013.

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