Network-based analysis of fatal comorbidities of COVID-19 and potential therapeutics

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Abstract

Coronavirus disease 2019 (COVID-19) is a highly contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The case fatality rate is significantly higher in older patients and those with diabetes, cancer or cardiovascular disorders. The human proteins, angiotensin-converting enzyme 2 (ACE2) and basigin (BSG), are involved in high-confidence host-pathogen interactions with proteins from SARS-CoV-2. We applied the random walk with restart method on the human interactome to construct a significant sub-network around these two proteins. The protein-protein interaction sub-network captures the effects of viral invasion on fatal comorbidities through critical pathways. The ‘insulin resistance’, ‘AGE-RAGE signaling pathway in diabetic complications’ and ‘adipocytokine signaling pathway’ were found in all fatal comorbidities. The association of these critical pathways with aging and its related diseases explains the molecular basis of COVID-19 fatality. We further investigated the critical proteins and corresponding pathways, and identified drugs that have effects on these proteins/pathways based on gene expression studies. We particularly focused on drugs that significantly downregulate ACE2 along with other critical proteins identified by the network-based approach. Among them, COL-3 (also known as incyclinide) had earlier shown activity against acute lung injury and acute respiratory distress, while entinostat and mocetinostat have been investigated for non-small-cell lung cancer. We propose that these drugs can be repurposed for COVID-19.

Keywords: SARS-CoV-2; coronavirus; disease comorbidity analysis, protein-protein interactions; biological networks; biological pathways; drug repurposing

1 Introduction

The outbreak of novel coronavirus disease, called COVID-19, started in Wuhan province of China in December 2019 and rapidly spread to other parts of the world (Huang et al., 2020). The World Health Organization declared it as a pandemic as it infected over a million people across more than 100 countries, causing thousands of deaths (Bedford et al., 2020). Coronaviruses have caused two major pandemics in the past - severe acute respiratory syndrome (SARS), which originated from China in 2003, and Middle East respiratory syndrome (MERS), which originated from Saudi Arabia in 2012 (Drosten et al., 2003; Zaki et al., 2012). Several research groups are working on the development of drugs and vaccines against these viruses. There are several ongoing clinical trials of drugs such as chloroquine and ritonavir (Dong et al., 2020). However, currently there are no therapeutics which have been considered safe and effective for the treatment of COVID-19 (Cao et al., 2020).

The viral entry into human cells is carried out by the spike (S) protein of SARS-CoV-2. Two human proteins have been identified as host receptors for the viral invasion into human cells - angiotensin-converting enzyme 2 (ACE2) (Zhou et al., 2020a) and basigin (BSG/CD147) (Wang et al., 2020b). Apart from that, a recent paper identified a number of human proteins involved in host-pathogen protein-protein interactions with the virus (Gordon et al., 2020). Another recent publication identified a number of host-pathogen interactions for SARS-CoV-2 by assembling CoV-associated host proteins from four known human coronaviruses (SARS-CoV, MERS-CoV, HCoV-229E, and HcoV-NL63) (Zhou et al., 2020b).

It has been observed that COVID-19 has more severe effects on older people than younger people (Yang et al., 2020b). Apart from causing pneumonia, COVID-19 may also cause damage to other organs such as the heart, liver, and kidneys, as well as to organ systems such as the circulatory and the immune system. Patients eventually die of multiple organ failure, shock, acute respiratory distress syndrome, heart failure and renal failure. Diseases like diabetes, cardiovascular disorders and cancer are risk factors for severe patients compared to non-severe patients (Yang et al., 2020a). Network-based approach has been effectively used to understand the disease mechanism and comorbidities of SARS and HIV infections (Moni and Liò, 2014). In this work, we first re-constructed a host protein-protein interaction (PPI) network based on known information about initial host contacts of the virus and their neighborhood. Analysis of this PPI network and subsequent pathway analysis explained the molecular basis of fatal comorbidities of COVID-19 with other diseases like (diabetes, cardiovascular diseases and cancer). We identified important

proteins and pathways associated with these diseases and proposed drugs that can be repurposed for COVID-19 using gene expression data of drug molecules and heterogeneous network information.

2 Methods

2.1 Data

The study is based on an integrated analysis of PPI, disease associations and drug associations. The PPI data was obtained from a recent study (Cheng et al., 2019) which integrates experimentally validated interactions from 15 bioinformatics and systems biology databases. The disease-gene association information was obtained by considering high confidence experimentally validated associations reported in DisGeNet (Piñero et al., 2017), OMIM (Amberger et al., 2015), ClinVar (Landrum et al., 2016) and PheGenI (Ramos et al., 2014) databases. The disease hierarchy from Disease Ontology database (Kibbe et al., 2015) was used as the reference for disease classification. The drug-target association information for approved and investigational drugs was obtained from the DrugBank (Wishart et al., 2018).

2.2 Construction of COVID-19 related sub-network

The host PPI network associated with COVID-19 infection, called COVID-19 host PPI network, was constructed by considering the PPIs around the SARS-CoV-2 spike protein receptors in the human interactome. The two reported receptors, ACE2 (Zhou et al., 2020a) and BSG (Wang et al., 2020b), were considered as seed nodes for the execution of random walk with restart (RWR) algorithm on the human interactome. RWR is a ranking algorithm, which engages a walker to inspect the global network to determine the closeness between two proteins in the PPI network (Chen and Xu, 2015; Li et al., 2017; Das et al., 2019). The walker starts its journey from the reported receptors (seed nodes) and travels randomly to all other proteins in the PPI network, but is forced to return to the seed proteins with a restart probability, r, of 0.7. The closeness of the proteins to the reported receptors is computed as a probability vector, P_i, which represents the probability of each protein in the PPI network at each step i as

$$P_{i+1} = (1 - r)A^T P_i + rP_0 \quad (1)$$

where, P_0 is the initial probability vector and A^T is the transpose of the column-normalized adjacency matrix of the network. P_{i+1}, the final outcome of the RWR calculations, is considered to be converged when $(P_{i+1}) - P_i < 1*10^{-5}$, indicating that the probability vector was stable. The significant proteins from RWR analysis were filtered based on RWR score cutoff of 0.005.

The RWR algorithm is highly dependent on the network topology and may pick up several proteins unrelated to the seed proteins (Li et al., 2017). To screen these false positives, a permutation test was performed where RWR was employed 1000 times, each time using randomly generated seed proteins from the PPI network (Chen and Xu, 2015; Li et al., 2017; Das et al., 2019). A *p-value* for each protein predicted by RWR was calculated, which captures the significance of the predicted proteins. The *p-value* was computed as

$$p\text{-}value(prot) = \Theta/1000 \quad (2)$$

Here, Θ represented the number of RWRs on randomly generated seed proteins in which the probability of the RWR-predicted protein, *prot*, is higher than that of the seed nodes. Proteins with *p-value* lower than 0.05 were considered statistically significant for further analysis (Li et al., 2017). The sub-network of human interactome obtained from the RWR analysis captures the significant neighborhood of the viral receptors, which can be analyzed to understand the mechanism of viral invasion.

2.3 Enrichment analysis

The gene ontology (GO) enrichment and pathway analysis were carried out using the gene set enrichment analysis web server, Enrichr (Kuleshov et al., 2016). The significant GO terms and KEGG pathways (Kanehisa et al., 2016) were identified by using adjusted *p*-value cut-off of 0.05. The GO terms of biological processes were summarized and the relationship between them was analyzed using the REVIGO webserver (Supek et al., 2011).

2.4 Identification of drug molecules using gene expression data

Drug Gene Budger (Wang et al., 2019) was used to explore drugs and small molecules in L1000 data (Subramanian et al., 2017), which significantly regulate ACE2 expression (both upregulate and downregulate) along with other critical proteins of the COVID-19 host network. Small molecules that lead to differential gene expression of important proteins, captured by $\log_2$ fold change (LFC) higher than 1.5 for upregulation and less than -1.5 for downregulation, were considered for further analyses. Drugs which are responsible for significant over expression of ACE2 can increase the risk of COVID-19. On the other hand, drugs which significantly downregulate the ACE2 expression were further explored for their potential therapeutic application against COVID-19. Mechanism of action, clinical trial stages and structural details of drugs were analysed using DrugBank (Wishart et al., 2018), PubChem (Kim et al., 2019), L1000FWD (Wang et al., 2018) and ClinicalTrials.gov (https://clinicaltrials.gov/). Drugs which were approved by FDA or undergoing clinical trials were considered for further analysis.

All scripts were written in Python and Perl, while network analysis was performed in Cytoscape (Shannon et al., 2003).

3 Results and discussion

We have analyzed the biological processes, pathways and disease comorbidities of COVID-19 by considering the protein-protein interactions around the point of viral entry into the host cell through its receptors, ACE2 and BSG. The PPI neighborhood of ACE2 and BSG obtained from RWR (COVID-19 host PPI network) comprises of 59 proteins and 121 edges, as shown in Figure 1.

The progression of the viral infection affects human health through various biological processes carried out by the proteins in the neighborhood of the receptors in the human interactome. We identified the significant GO terms for biological processes associated with the proteins in the COVID-19 host PPI. The statistically significant biological processes and the relationship between them through the COVID-19 host PPI are shown in Figure S1. The processes are colored (Figure S1) based on the dispensability score obtained from REVIGO, where higher scores are represented by darker shades of gray (Supek et al., 2011). The COVID-19 host PPI comprises of proteins that regulate critical metabolic processes of the human body. These include the processes involved in immune response, glucose metabolism, vasoconstriction, protein degradation and post-translational modifications. Although the molecular basis of the effect of COVID-19 on these biological processes can be validated experimentally through protein assays and gene expression data analysis, the network-based approach provides a systems level understanding of the effect on the interconnected biological processes.

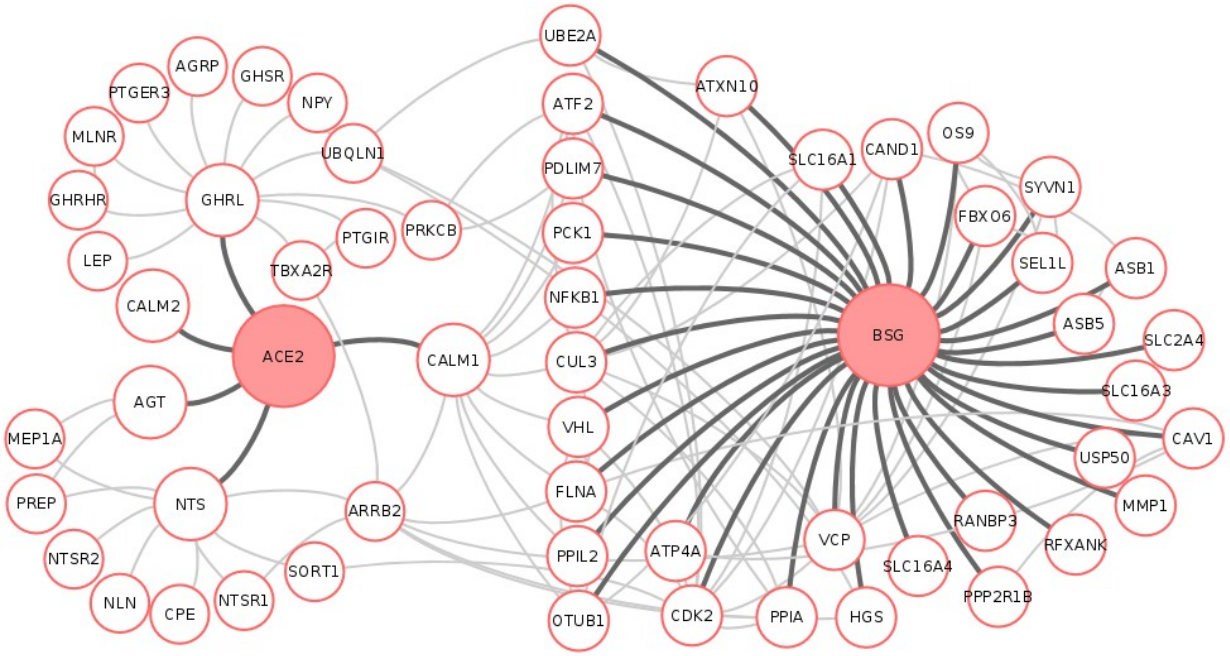

Figure 1: COVID-19 host protein-protein interaction network. The receptors of SARS-CoV2, ACE2 and BSG, and the edges connecting them to their immediate neighbors are highlighted.

3.1 Disease Comorbidity

The impact of COVID-19 has been observed to be severe in patients with cancer, cardiovascular disease, diabetes and gastrointestinal disorders (Fang et al., 2020; Huang et al., 2020; Wang et al., 2020a, 2020d). The fatalities in these critical care patients have been mostly due to the original comorbidity leading to multiple organ failure (Liang et al., 2020; Wang et al., 2020d). Till date, there are no proven therapeutics for the treatment of patients suffering from COVID-19 (Cao et al., 2020). These complex conditions alter many biological processes and pathways in the human body. Here, we investigate the effect of COVID-19 through the human protein-protein interactions and analyze the important pathways affected in the severe comorbidities due to the infection. Figure 2 shows the disease association of the PPI network for respiratory diseases, cardiovascular diseases, cancers, glucose metabolism disorders, kidney diseases and gastrointestinal diseases; the diseases are colored based on the disease group. The genes associated with the disease groups are shown in Table 1 and the detailed association with each disease within the disease group is given in supplementary table S1. The high comorbidity of COVID-19 with several diseases of different disease groups can be attributed to the critical genes that are associated with multiple disease groups. These include Angiotensinogen (AGT), Nuclear factor kappa B subunit 1 (NFKB1), Caveolin 1 (CAV1), Leptin (LEP), Ghrelin (GHRL) and Von Hippel-Lindau (VHL).

AGT is associated with the most number of diseases, which belong to the categories of cardiovascular, respiratory, glucose metabolism, kidney and gastrointestinal diseases. It is the only precursor of all angiotensin peptides and regulates blood pressure and homeostasis of water and sodium through the renin–angiotensin system (RAS) (Lu et al., 2016). The RAS pathway is known to be associated with cardiovascular diseases, respiratory diseases, glucose metabolism, kidney disease and gastrointestinal diseases (Marshall, 2003; Remuzzi et al., 2005; Joseph et al., 2018; Wu et al., 2018). NFKB1 is a transcription factor of proinflammatory molecules and is an important regulator of innate and adaptive immunity, cell proliferation, stress responses and apoptosis. It is therefore associated with pathogenic infections, diabetes, kidney and liver diseases, and cancer (Patel and Santani, 2009; Cartwright et al., 2016, 1). CAV1 is a membrane protein associated with endocytosis, extracellular matrix organization, cholesterol distribution, cell migration and signaling (Nwosu et al., 2016). It is associated with diabetes, cancer and cardiovascular diseases. LEP and GHRL regulate the energy homeostasis in the body by storage of fat and appetite regulation respectively (Margetic et al., 2002; Sato et al., 2012). These are associated with glucose metabolism disorders, gastrointestinal disorders and some forms of cancer. VHL is a tumor suppressor gene associated with many forms of cancer (Kim and Kaelin, 2004).

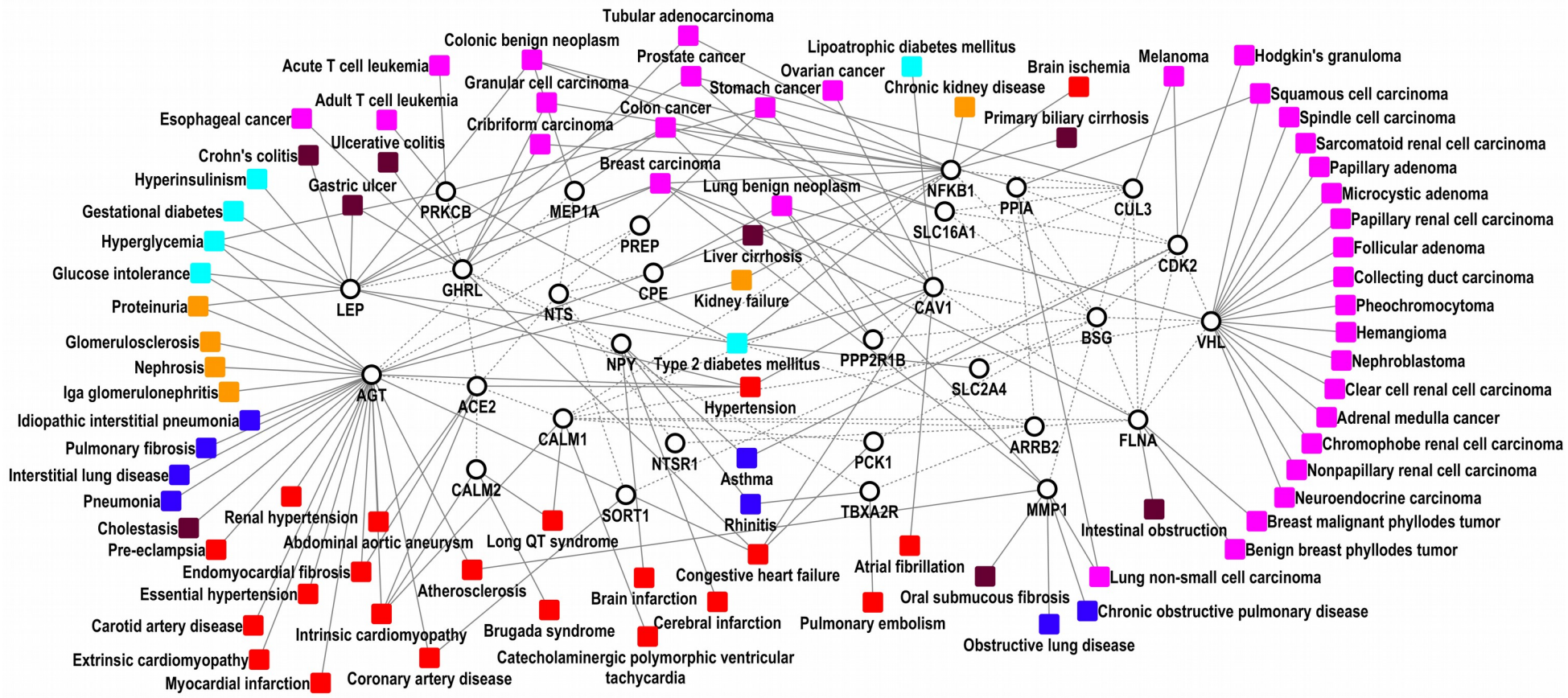

Figure 2: PPI associated with the COVID-19 infection and diseases associated with them. The proteins are represented by circles and diseases by squares. The diseases are colored based on the type of disease - respiratory disease (blue), cardiovascular disease (red), cancer (purple), glucose metabolic disorder (cyan), kidney disorder (orange) and gastrointestinal disorder (brown). The edges between proteins (from PPI) are represented by dashed lines and gene-disease association by solid lines.

Table 1: The disease groups affected by the COVID-19 host PPI network.

Disease group	Associated genes in COVID-19 host PPI
Respiratory system disease	CDK2, NPY, MMP1, AGT, TBXA2R
Glucose metabolism disease	LEP, AGT, PRKCB, SLC2A4, CAV1, NFKB1
Cancer	VHL, PPP2R1B, MMP1, CPE, MEP1A, SLC16A1, LEP, NFKB1, FLNA, PPIA, CAV1, CUL3, CDK2, PRKCB, PREP, GHRL
Cardiovascular system disease	ACE2, AGT, CALM1, CALM2, CAV1, GHRL, PCK1, LEP, MMP1, SORT1, TBXA2R, NFKB1, NPY
Kidney disease	AGT, NFKB1, LEP
Gastrointestinal system disease	AGT, NFKB1, MMP1, GHRL, LEP, FLNA

For all the disease groups with fatal comorbidity, we identified the pathways enriched by their associated genes in the COVID-19 host PPI network. The significant pathways identified are shown in Figure 3 and the detailed list of pathways is provided in supplementary table S2. There are three critical pathways that are affected in all severe disease groups – ‘insulin resistance’, ‘AGE-RAGE signaling pathway in diabetic complications’ and ‘adipocytokine signaling pathway’. The progression of COVID-19 infection leading to severe conditions and fatality can be explained based on these critical pathways.

Insulin resistance: Insulin resistance is a characteristic feature of the most prevalent metabolic disorder, type 2 diabetes, and is associated with cardiovascular diseases and cancer (Yaribeygi et al., 2019). Hyperinsulinemia can lead to hypertension by the activation of the sympathetic nervous system, renal sodium retention, altered transmembrane cation transport and growth-promoting effects of vascular smooth muscle cells (McFarlane et al., 2001). Hypertension along with dyslipidemia caused by insulin resistance can lead to cardiovascular conditions, especially coronary artery disease (Ginsberg, 2000). The increase in level of insulin can also stimulate the synthesis of sex steroids that can promote cellular proliferation and inhibit apoptosis, leading to cancer (Arcidiacono et al., 2012; Orgel and Mittelman, 2013). Insulin resistance can also be associated with cancer through the overproduction of reactive oxygen species that can damage DNA, contributing to mutagenesis and carcinogenesis.

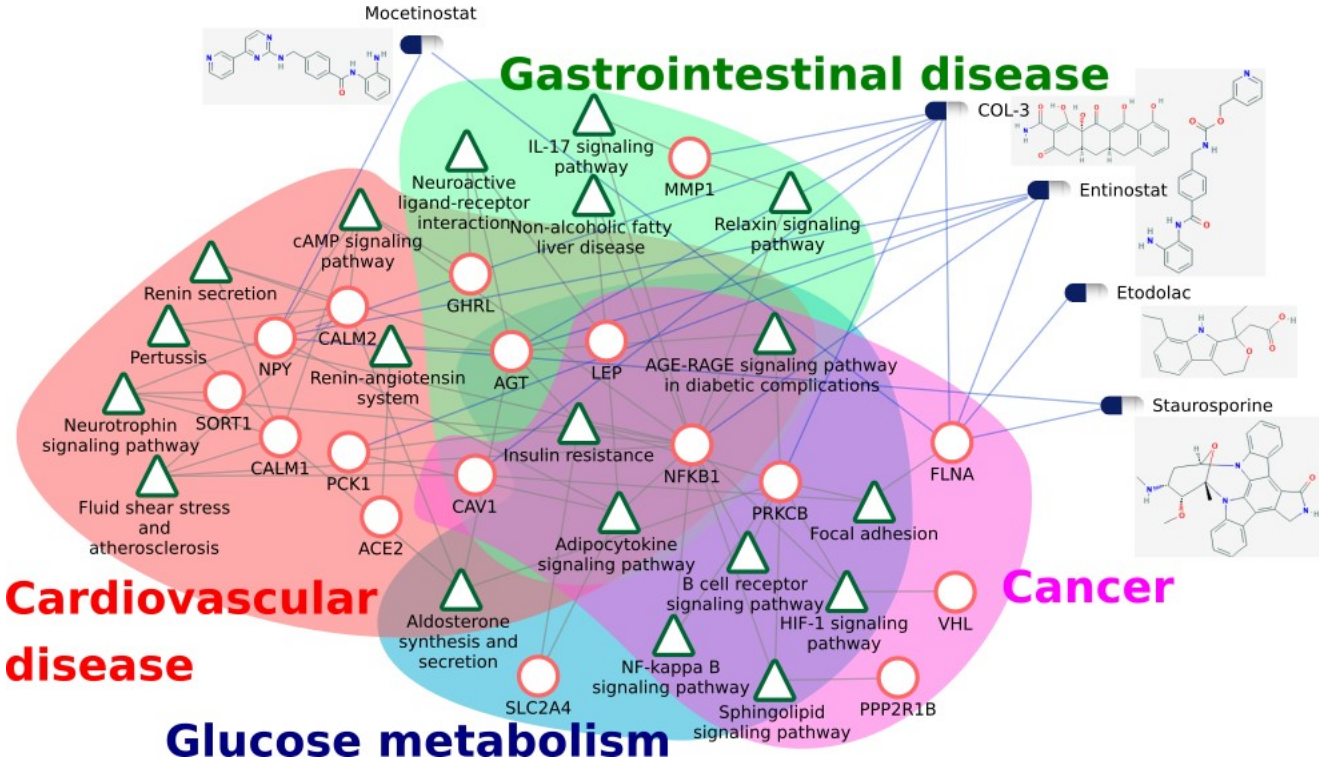

Figure 3: Heterogeneous network comprising of the pathways (green triangles) responsible for fatal comorbidities related to COVID-19, genes (red circles) and drugs (as capsules) which affect them. All drugs shown here are also connected with ACE2 as they downregulate ACE2 gene expression but the edges between ACE2 and the drugs are not shown here for simplicity.

AGE-RAGE signaling pathway in diabetic complications: Advanced glycation end products (AGEs) are the products of non-enzymatic glycation and oxidation of proteins and lipids that accumulate in diabetes (Singh et al., 2001; Ramasamy et al., 2011). Increased levels of AGEs, especially carboxymethyllysine (CML), have been observed to be associated with atherosclerosis, coronary artery disease and heart failure (Hegab et al., 2012). The indirect vascular effects of elevated AGEs such as coronary dysfunction, atherosclerosis and thrombosis, and their direct effects on myocardium, lead to heart failure. The increased levels of these highly reactive AGEs induce persistent inflammation and oxidative stress, which lead to cancer (Turner, 2015; Schröter and Höhn, 2018).

Adipocytokine signaling pathway: Adipocytokines are secreted by the adipose tissues, which signal key metabolic organs such as liver, muscle and pancreas, to maintain metabolic homeostasis through the adipocytokine signaling pathway (Cao, 2014). Leptin is the major adipocytokine which controls appetite and is associated with obesity. However, it also stimulates oxidative stress, inflammation, thrombosis, arterial stiffness, angiogenesis and atherogenesis. It is associated with diabetes, cardiovascular conditions, chronic kidney diseases and cancer (Dutta et al., 2012; Katsiki et al., 2018).

It can be observed that all the three pathways common to the fatal comorbidities are also related to aging (Fink et al., 1983; Ryan, 2000; Gulcelik et al., 2013; Chaudhuri et al., 2018). This is in congruence with the age-wise distribution of case fatality rate of COVID-19 observed in China and Italy (Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020; Onder et al., 2020). The case-fatality rate for patients older than 80 years is as high as 20% whereas it reduces to less than 1% for patients younger than 60 years of age. Aging leads to altered levels of insulin, AGEs and leptin in the body, which are further affected in COVID-19 patients through these pathways.

Apart from these common critical pathways discussed above, there are some specific pathways associated with the fatal comorbidities.

Glucose metabolism disorder: The genes involved in COVID-19 host PPI are associated with glucose metabolism diseases (Figure 2 and Table 1). They regulate ‘B cell receptor signaling pathway’, ‘NF-kappa B signaling pathway’, ‘aldosterone synthesis and secretion’, ‘HIF-1 signaling pathway’ and ‘sphingolipid signaling pathway’.

Cardiovascular diseases: The genes that can lead to cardiovascular diseases (Figure 2 and Table 1) are involved in pathways that are responsible for ‘renin secretion’, ‘renin-angiotensin system’,

‘fluid shear stress and atherosclerosis’, ‘aldosterone synthesis and secretion’, ‘neurotrophin signaling pathway’ and ‘cAMP signaling pathway’.

Gastrointestinal diseases: The pathways of gastrointestinal diseases are ‘relaxin signaling pathway’, ‘IL-17 signaling pathway’, ‘non-alcoholic fatty liver disease (NAFLD)’ and ‘neuroactive ligand-receptor interaction’. The genes that can lead to gastrointestinal diseases are shown in Table 1 and Figure 2.

Cancer: The cancer pathways associated with the COVID-19 host PPIs are ‘HIF-1 signaling pathway’, ‘sphingolipid signaling pathway’, ‘B cell receptor signaling pathway’, ‘NF-kappa B signaling pathway’ and ‘focal adhesion’.

3.2 Potential drugs for COVID-19

The spike protein of SARS-CoV-2 mainly binds to the target cells through ACE2 (Fang et al., 2020). The ACE2 is expressed in epithelial cells of the lungs, intestine, kidneys, and blood vessels (Wan et al., 2020). Studies based on SARS-CoV infected mice model suggest that over-expression of human ACE2 enhanced disease severity (Yang et al., 2007; Monteil et al., 2020; Sommerstein et al., 2020). Drug Gene Budger (DGB) (Wang et al., 2019) was used to explore existing drugs and small molecules that regulate ACE2 expression from L1000 data (Subramanian et al., 2017). The analysis of expression data helps in understanding the importance of proteins and pathways identified in this study and their relationship with SARS-CoV-2 receptors. The objective is to identify drugs that can increase the chances of COVID-19 infection in patients with comorbidites and explore the existing drugs which can be repurposed for COVID-19.

Drugs that increases the possibility of COVID-19: Drugs that are responsible for overexpression of ACE2 can increase the probability of COVID-19 infection. Age and gender are other important determinants of ACE2 expression as it is observed that the expression is significantly higher in older people and males (Fernández-Atucha et al., 2017; Walters et al., 2017). The ACE2 expression is substantially increased in patients with type 1 and type 2 diabetes, who are treated with ACE inhibitors like moexipril (Drug Bank id: DB00691) (Chrysant and Nguyen, 2007) or angiotensin II type-I receptor blockers (ARBs). Hypertension is also treated with ACE inhibitors and ARBs, which results in an upregulation of ACE2. ACE2 can also be increased by thiazolidinediones and ibuprofen (Fang et al., 2020). Based on gene-expression data from L1000, we identified few additional drugs which are responsible for significant over expression of ACE2. We hypothesise that these drugs can increase the chance of COVID-19. The ACE2 expression is significantly upregulated by Danusertib (LFC 1.8), which is studied for hormone refractory prostate cancer (Meulenbeld et al., 2013). Trichostatin A is an anti-cancer drug, which also possesses antifungal and

antibiotic properties. It inhibits the activation of the PI3K/Akt and ERK1/2 pathways (Ma et al., 2015) and significantly upregulates ACE2 expression (LFC 2).

Drugs that downregulate ACE2 expression: The drugs which significantly downregulate ACE2 activity, can be considered as probable therapeutics against COVID-19. Drugs that significantly downregulate ACE2 gene expression and at the same time inhibit other important proteins and pathways of the host sub-network (shown in figure 3) were identified from L1000 dataset (Subramanian et al., 2017). Some recent articles indicate that hydroxychloroquine and chloroquine inhibit terminal glycosylation of ACE2 (Vincent et al., 2005; Wang et al., 2020c). As a result, ACE2 becomes less efficient in interacting with the SARS-CoV-2 spike protein, thus inhibiting viral entry. It will be interesting to identify other drugs that affect ACE2.

The full list of drugs that downregulate ACE2 and at least one important protein of the COVID-19 host PPI network is shown in Table 2. Here, some of them are discussed in detail. COL-3 (also known as incyclinide or CMT-3) has been extensively studied as a potential new therapeutic agent for allergic conditions, inflammatory conditions (i.e., arthritis, acute respiratory distress syndrome, septic shock syndrome, acne and rosacea), neoplastic diseases (i.e., colon carcinoma, prostate cancer) and infectious (fungal) diseases. COL-3 has been used in trials for HIV infection and brain and central nervous system tumors (Viera et al., 2007). Most importantly, COL-3 has shown promising results against acute lung injury and acute respiratory distress in animal models (Bosma et al., 2010). It significantly downregulates ACE2 (LFC -1.8) and other important proteins in the COVID-19 host PPI network, including AGT, CAV1, FLNA, MMP1, NPY and PRKCB (see Figure 3).

Interestingly, the list of drugs include investigational anti-cancer drugs entinostat, mocetinostat and alvespimycin. Entinostat and mocetinostat are benzamide-containing histone deacetylase (HDAC) inhibitors that downregulate ACE2 expression (LFC -1.8 and -1.7 respectively as shown in Table 2). Entinostat (Connolly et al., 2017) is under investigation for the treatment of non-small-cell lung cancer and epigenetic therapy. It is also found to downregulate other important proteins in the COVID-19 host PPI network, including AGT, FLNA, NFKB, NPY and PCK1. Mocetinostat (Gerson et al., 2018) is currently in phase 2 clinical trials for the treatment of various lymphoid and myeloid malignancies (Sheikh et al., 2016). Alvespimycin is a derivative of geldanamycin, which is known to reduce acute respiratory distress syndrome (Lancet et al., 2010; Wang et al., 2017). Alvespimycin inhibits HSP90 and its regulation of cell signalling pathways. It downregulates ACE2 expression (LFC -2.11) and at the same time significantly downregulates CAV1, FLNA, MMP1, NPY which are part of the COVID-19 host PPI network. In fact, geldanamycin itself downregulates ACE2 (LFC -1.2). However, Alvespimycin has been terminated in phase 2 clinical trials.

Staurosporine is a natural product isolated from *Streptomyces staurosporeus* which downregulates ACE2 expression (LFC -1.5) (Omura et al., 1977; Tamaoki et al., 1986).

Etodolac (Humber, 1987) is a non-steroidal anti-inflammatory moderate painkiller drug used in rheumatoid arthritis and osteoarthritis. It significantly downregulates ACE2 expression (LFC -1.5). The anti-inflammatory effects of etodolac result from inhibition of the cyclooxygenase enzymes (COX), specially COX-2. COX-2 is part of the NFKB pathway, an important pathway of the COVID-19 host PPI sub-network. It was also found to downregulate FLNA of the host sub-network, which is also part of the NFKB pathway.

Table 2: Drugs from L1000 dataset which significantly downregulate ACE2 along with other critical proteins of the COVID-19 related human PPI sub-network (Figure 3). The $\log_2$ fold change (LFC) data is shown only for ACE2.

S. No.	Drug name	Host genes downregulated	LFC for ACE2	Status of drug
1.	COL-3	ACE2, AGT, CAV1, FLNA, MMP1, NPY, PRKCB	-1.8	Phase 2 completed
2	Entinostat	ACE2, AGT, FLNA, NFKB, NPY, PCK1	-1.8	Phase 3 recruiting
3	Mocetinostat	ACE2, FLNA, NPY	-1.7	Phase 2 completed
4	Staurosporine	ACE2, FLNA, NPY	-1.5	Phase 2 completed
5	Etodolac	ACE2, FLNA	-1.6	FDA approved

Conclusions

Diseases are usually regulated by a complex network of protein-protein interactions. We have used the human PPI network to explain the molecular basis of comorbidities between COVID-19 and other diseases. We started with two high confidence host contacts of SARS-CoV-2, viz., ACE2 and BSG, and then reconstructed the local network around them using the RWR method. We could identify the proteins and pathways that are implicated in cancer, cardiovascular disease, diabetes and gastrointestinal disorders from this local network. We identified 5 drugs that can significantly downregulate the primary receptor of SARS-Cov-2, ACE2, along with other important proteins of the host PPI sub-network. Among them, COL-3 has previously shown activity against acute lung injury and acute respiratory distress, while entinostat and mocetinostat are in clinical trials for non-small-cell lung cancer. We opine that these drugs can be investigated further for their therapeutic value and repurposed against COVID-19.

The inferences presented in this work are based on holistic approach to understand the critical comorbidities of COVID-19 based on protein-protein interactions. The molecular basis of comorbidities and potential drugs proposed here are preliminary indications requiring experimental validations.

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Supplementary Data

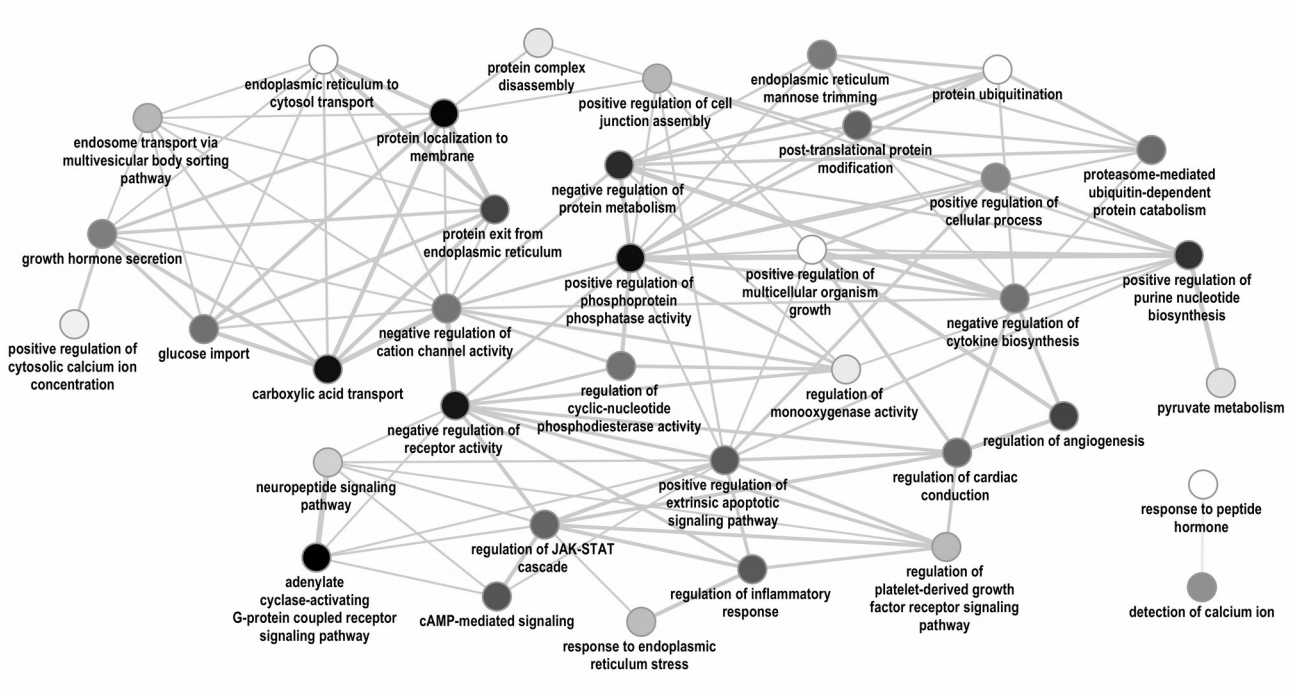

Figure S1: Biological processes enriched by the proteins associated with the COVID-19 infection. The processes are colored based on the dispensability score obtained from REVIGO.

Table S1: The diseases associated with the COVID-19.

Disease group	disease_Name	Overlapping gene
Glucose metabolism disease	hyperinsulinism	LEP
	hyperglycemia	AGT, PRKCB, LEP
	glucose intolerance	LEP, AGT
	diabetes mellitus	SLC2A4, LEP, CAV1, NFKB1, PRKCB
	gestational diabetes	LEP
	type 2 diabetes mellitus	SLC2A4, LEP, CAV1, NFKB1, PRKCB
	lipoatrophic diabetes mellitus	CAV1
Crbohydrate metabolic disorder	hyperinsulinemic hypoglycemia	SLC16A1
	primary hyperoxaluria	NFKB1
Cancer	papillary adenoma	VHL
	lung benign neoplasm	PPP2R1B, VHL, MMP1, CPE
	microcystic adenoma	VHL
	colonic benign neoplasm	MEP1A, SLC16A1, LEP, NFKB1
	pheochromocytoma	VHL
	follicular adenoma	VHL
	hemangioma	VHL

	benign breast phyllodes tumor	FLNA
	lung non-small cell carcinoma	PPIA, MMP1
	adrenal medulla cancer	VHL
	ovarian cancer	CAV1
	prostate cancer	LEP, CAV1, CUL3
	Hodgkin's granuloma	CDK2
	adult T-cell leukemia	PRKCB
	acute T cell leukemia	PRKCB
	colon cancer	MEP1A, PPP2R1B, SLC16A1, LEP, NFKB1
	stomach cancer	PPIA, CAV1, PREP, PRKCB
	esophageal cancer	GHRL
	nephroblastoma	VHL
	nonpapillary renal cell carcinoma	VHL
	collecting duct carcinoma	VHL
	papillary renal cell carcinoma	VHL
	clear cell renal cell carcinoma	VHL
	chromophobe renal cell carcinoma	VHL
	sarcomatoid renal cell carcinoma	VHL
	breast malignant phyllodes tumor	FLNA
	breast carcinoma	FLNA, CAV1, MMP1, NFKB1, LEP, GHRL
	cribriform carcinoma	GHRL, NFKB1
	melanoma	CDK2, CUL3
	squamous cell carcinoma	PPIA, VHL
	spindle cell carcinoma	VHL
	neuroendocrine carcinoma	VHL
	tubular adenocarcinoma	GHRL, NFKB1
	granular cell carcinoma	GHRL, NFKB1
Disease of mental health	syndromic X-linked intellectual disability	UBE2A
	autistic disorder	LEP, PRKCB
	dissociative amnesia	PREP
	amnestic disorder	PREP
	neurotic disorder	GHRL, NPY
	schizophrenia	CAV1, BSG, ARRB2, GHRL, PCK1, CALM1, PPIA, LEP, CUL3, NTSR1, NTS, PTGER3, NPY
	mental depression	PRKCB, ARRB2, AGT, CALM2, NPY, LEP, GHRL, NTS
	major depressive disorder	GHRL, PRKCB, NPY
	endogenous depression	GHRL, PRKCB, NPY
	melancholia	GHRL, NPY

	bipolar disorder	ARRB2, AGT, PREP, CALM2
	alcohol use disorder	GHSR, NPY
	phencyclidine abuse	CALM2, CALM1
	cocaine abuse	GHRL, CALM1, NPY, CALM2
	cannabis abuse	CALM1, CALM2
	opiate dependence	LEP
	heroin dependence	LEP
	hallucinogen dependence	CALM1, CALM2
Cardiovascular system disease	intrinsic cardiomyopathy	ACE2, AGT, CALM1, CALM2,
	long QT syndrome	CALM1, CALM2
	endomyocardial fibrosis	AGT, ACE2
	extrinsic cardiomyopathy	AGT
	Brugada syndrome	CALM2
	atrial fibrillation	CAV1
	catecholaminergic polymorphic ventricular tachycardia	CALM1
	congestive heart failure	CAV1, GHRL, AGT, PCK1
	hypertension	LEP, ACE2, CAV1, AGT
	pre-eclampsia	AGT
	essential hypertension	AGT
	renal hypertension	AGT
	atherosclerosis	AGT, MMP1
	coronary artery disease	AGT, SORT1
	myocardial infarction	AGT
	abdominal aortic aneurysm	AGT, ACE2
	pulmonary embolism	TBXA2R
	brain ischemia	NFKB1
	carotid artery disease	AGT
	brain infarction	NPY
	cerebral infarction	NPY
Respiratory system disease	asthma	CDK2, NPY
	obstructive lung disease	MMP1
	chronic obstructive pulmonary disease	MMP1
	interstitial lung disease	AGT
	pulmonary fibrosis	AGT
	pneumonia	AGT
	idiopathic interstitial pneumonia	AGT
	rhinitis	TBXA2R, NPY
Skin disease	Stevens-Johnson syndrome	CAV1, FBXO6, VCP, PTGER3
	dermatitis	PTGER3
	epidermolysis bullosa	MMP1

Muscular disease	congenital diaphragmatic hernia	AGT
	distal myopathy	VCP
	limb-girdle muscular dystrophy	VCP
Connective tissue disease	osteogenesis imperfecta	GHSR, GHRHR
	multiple epiphyseal dysplasia	FLNA
	Marfan syndrome	FLNA
	familial partial lipodystrophy	CAV1
Kidney disease	kidney failure	AGT, NFKB1
	chronic kidney disease	NFKB1
	glomerulosclerosis	AGT
	IgA glomerulonephritis	AGT
	proteinuria	AGT, LEP
	nephrosis	AGT
Immune system disease	autoimmune hepatitis	LEP
	limited scleroderma	CAV1
	diffuse scleroderma	CAV1
	common variable immunodeficiency	NFKB1
	MHC class II deficiency	RFXANK
Hematopoietic system disease	blood platelet disease	TBXA2R
	anemia	AGT
	primary polycythemia	VHL
Gastrointestinal system disease	liver cirrhosis	AGT, NFKB1
	primary biliary cirrhosis	NFKB1
	cholestasis	AGT
	oral submucous fibrosis	MMP1
	ulcerative colitis	GHRL
	Crohn's colitis	LEP
	intestinal obstruction	FLNA
	gastric ulcer	LEP, GHRL
Nervous system disease	primary open angle glaucoma	CAV1
	diabetic retinopathy	AGT
	autosomal dominant cerebellar ataxia	ATXN10
	amyotrophic lateral sclerosis	VCP
	Alzheimer's disease	SLC2A4, LEP, CALM1, NPY
	hydrocephalus	FLNA
	visual epilepsy	LEP, GHRL, AGT, NPY
	focal epilepsy	NPY
	temporal lobe epilepsy	NPY
	Charcot-Marie-Tooth disease	VCP
Other diseases	obesity	LEP, GHRL, AGRP, PCK1, CPE
	morbid obesity	LEP

	hypogonadism	LEP
	CREST syndrome	CAV1
	abdominal obesity-metabolic syndrome 1	LEP
	polycystic ovary syndrome	LEP, PTGER3
	FG syndrome	FLNA
	fatty liver disease	LEP
	periventricular nodular heterotopia	FLNA

Table S2: Pathways enriched in cancer, cardiovascular diseases and glucose metabolism disease.

Cancer	
Term	**Genes**
HIF-1 signaling pathway	PRKCB;VHL;NFKB1
Sphingolipid signaling pathway	PPP2R1B;PRKCB;NFKB1
Long-term depression	PPP2R1B;PRKCB
Adipocytokine signaling pathway	LEP;NFKB1
B cell receptor signaling pathway	PRKCB;NFKB1
Leishmaniasis	PRKCB;NFKB1
Hepatitis C	PPP2R1B;CDK2;NFKB1
Hepatitis B	PRKCB;CDK2;NFKB1
Salmonella infection	FLNA;NFKB1
Small cell lung cancer	CDK2;NFKB1
NF-kappa B signaling pathway	PRKCB;NFKB1
Amoebiasis	PRKCB;NFKB1
Prostate cancer	CDK2;NFKB1
AGE-RAGE signaling pathway in diabetic complications	PRKCB;NFKB1
Focal adhesion	PRKCB;CAV1;FLNA
Proteoglycans in cancer	PRKCB;CAV1;FLNA
Chagas disease (American trypanosomiasis)	PPP2R1B;NFKB1
Insulin resistance	PRKCB;NFKB1
Pathways in cancer	MMP1;PRKCB;CDK2;VHL;NFKB1
MAPK signaling pathway	PRKCB;FLNA;NFKB1
Human papillomavirus infection	PPP2R1B;CDK2;NFKB1
PI3K-Akt signaling pathway	PPP2R1B;CDK2;NFKB1
Cardiovascular disease	
Term	**Genes**
Adipocytokine signaling pathway	LEP;NPY;PCK1;NFKB1
Renin-angiotensin system	ACE2;AGT
Phototransduction	CALM1;CALM2
Renin secretion	CALM1;CALM2;AGT

Neurotrophin signaling pathway	SORT1;CALM1;CALM2;NFKB1
Pertussis	CALM1;CALM2;NFKB1
Fluid shear stress and atherosclerosis	CAV1;CALM1;CALM2;NFKB1
cAMP signaling pathway	NPY;GHRL;CALM1;CALM2;NFKB1
Aldosterone synthesis and secretion	CALM1;CALM2;AGT
Glucagon signaling pathway	CALM1;PCK1;CALM2
C-type lectin receptor signaling pathway	CALM1;CALM2;NFKB1
Insulin resistance	PCK1;AGT;NFKB1
Vascular smooth muscle contraction	CALM1;CALM2;AGT
Long-term potentiation	CALM1;CALM2
Amphetamine addiction	CALM1;CALM2
Insulin signaling pathway	CALM1;PCK1;CALM2
Neuroactive ligand-receptor interaction	TBXA2R;LEP;NPY;GHRL;AGT
Adrenergic signaling in cardiomyocytes	CALM1;CALM2;AGT
PPAR signaling pathway	MMP1;PCK1
Glioma	CALM1;CALM2
Gastric acid secretion	CALM1;CALM2
Cellular senescence	CALM1;CALM2;NFKB1
Salivary secretion	CALM1;CALM2
Tuberculosis	CALM1;CALM2;NFKB1
Alcoholism	NPY;CALM1;CALM2
IL-17 signaling pathway	MMP1;NFKB1
GnRH signaling pathway	CALM1;CALM2
Kaposi sarcoma-associated herpesvirus infection	CALM1;CALM2;NFKB1
Calcium signaling pathway	TBXA2R;CALM1;CALM2
Circadian entrainment	CALM1;CALM2
Phosphatidylinositol signaling system	CALM1;CALM2
Inflammatory mediator regulation of TRP channels	CALM1;CALM2
AGE-RAGE signaling pathway in diabetic complications	AGT;NFKB1
Melanogenesis	CALM1;CALM2
Human immunodeficiency virus 1 infection	CALM1;CALM2;NFKB1
Pathways in cancer	MMP1;CALM1;CALM2;AGT;NFKB1
Human cytomegalovirus infection	CALM1;CALM2;NFKB1
Ras signaling pathway	CALM1;CALM2;NFKB1
AMPK signaling pathway	LEP;PCK1
Oocyte meiosis	CALM1;CALM2
Relaxin signaling pathway	MMP1;NFKB1
Dopaminergic synapse	CALM1;CALM2
Estrogen signaling pathway	CALM1;CALM2
Apelin signaling pathway	CALM1;CALM2
Non-alcoholic fatty liver disease (NAFLD)	LEP;NFKB1

Oxytocin signaling pathway	CALM1;CALM2
cGMP-PKG signaling pathway	CALM1;CALM2
Alzheimer disease	CALM1;CALM2
Rap1 signaling pathway	CALM1;CALM2
Glucose metabolism disorder	
Term	**Genes**
Insulin resistance	PRKCB;SLC2A4;AGT;NFKB1
Adipocytokine signaling pathway	LEP;SLC2A4;NFKB1
AGE-RAGE signaling pathway in diabetic complications	PRKCB;AGT;NFKB1
B cell receptor signaling pathway	PRKCB;NFKB1
Leishmaniasis	PRKCB;NFKB1
NF-kappa B signaling pathway	PRKCB;NFKB1
Amoebiasis	PRKCB;NFKB1
Aldosterone synthesis and secretion	PRKCB;AGT
HIF-1 signaling pathway	PRKCB;NFKB1
Sphingolipid signaling pathway	PRKCB;NFKB1
AMPK signaling pathway	LEP;SLC2A4
Vascular smooth muscle contraction	PRKCB;AGT
Fluid shear stress and atherosclerosis	CAV1;NFKB1
Non-alcoholic fatty liver disease (NAFLD)	LEP;NFKB1
Hepatitis B	PRKCB;NFKB1
Influenza A	PRKCB;NFKB1
Chemokine signaling pathway	PRKCB;NFKB1
Focal adhesion	PRKCB;CAV1
Proteoglycans in cancer	PRKCB;CAV1
Human immunodeficiency virus 1 infection	PRKCB;NFKB1
Human cytomegalovirus infection	PRKCB;NFKB1
Ras signaling pathway	PRKCB;NFKB1
Pathways in cancer	PRKCB;AGT;NFKB1
MAPK signaling pathway	PRKCB;NFKB1
MicroRNAs in cancer	PRKCB;NFKB1
Neuroactive ligand-receptor interaction	LEP;AGT