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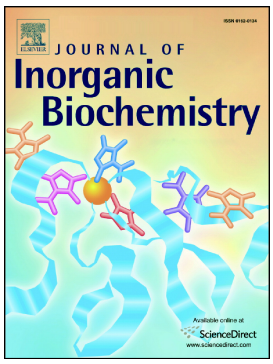

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PII: S0162-0134(21)00070-2

DOI: https://doi.org/10.1016/j.jinorgbio.2021.111423

Reference: JIB 111423

To appear in: *Journal of Inorganic Biochemistry*

Received date: 7 January 2021

Revised date: 16 February 2021

Accepted date: 8 March 2021

Please cite this article as: C.T. Chasapis, A.K. Georgiopoulou, S.P. Perlepes, et al., A SARS-CoV-2 –human metalloproteome interaction map, *Journal of Inorganic Biochemistry* (2021), https://doi.org/10.1016/j.jinorgbio.2021.111423

A SARS-CoV-2 –human metalloproteome interaction map

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Abstract

The recent pandemic caused by the novel coronavirus resulted in the greatest global health crisis since the Spanish flu pandemic of 1918. There is limited knowledge of whether SARS-CoV-2 is physically associated with human metalloproteins. Recently, high-confidence, experimentally supported protein-protein interactions between SARS-CoV-2 and human proteins were reported. In this work, 58 metalloproteins among these human targets have been identified by a structure-based approach. This study reveals that most human metalloproteins interact with the recently discovered SARS-CoV-2 orf8 protein, whose antibodies are one of the principal markers of SARS-CoV-2 infections. Furthermore, this work provides sufficient evidence to conclude that Zn^{2+} plays an important role in the interplay between the novel coronavirus and humans. First, the content of Zn-binding proteins in the involved human metalloproteome is significantly higher than that of the other metal ions. Second, a molecular linkage between the identified human Zn-binding proteome with underlying medical conditions that might increase the risk

of severe illness from the SARS-CoV-2 virus has been found. Likely perturbations of host cellular metal homeostasis by SARS-CoV-2 infection are highlighted.

Keywords

SARS-CoV-2, SARS-CoV-2 orf8, PPI, metalloproteome, metal homeostasis

Abbreviations

AD	Alzheimer's Disease
AMD	age macular degeneration
Cb5	cytochrome b5
CNS	central nervous system
COVID-19	corona virus disease 2019
CPS1	carbamoyl-phosphate synthase 1
CSNK2B	casein kinase II subunit beta
DNMT1	DNA methyltransferase 1
HNSCC	head and neck squamous cell carcinoma
HT	hypertension
ITGB1	integrin beta-1
KRCC	kidney renal clear cell carcinoma
PD	Parkinson's Diseases
PPI	protein-protein interaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIRT5	sirtuin-5
VPS11	vacuolar protein sorting-associated protein 11
ZNF318	zinc finger protein 318

1. Introduction

Since the beginning of the 21st century, the world has faced severe crises due to deadly viruses such as Ebola, Zika, avian influenza, AIDS, SARS, and MERS, to name a few. The large-scale explosion of these diseases' viral epidemics resulted from the evolution of pre-existing viruses or the appearance of new viral species, causing enormous damage to society in terms of health, economic and social crisis. Since December 2019, another virus named Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) has spread worldwide. The resulting pandemic is severely affecting global healthcare systems. Around a year after the pandemic began, about 110 million cases and over 2.4 million deaths have been reported worldwide [1]. COVID-19, the disease caused by the SARS-CoV-2, can result in pneumonia and respiratory failure that can be fatal, especially in the presence of other comorbidity factors [2]. The disease spread rapidly, causing a dramatic upheaval in people's everyday lives and in the local and global economies. Despite intense efforts by academic groups and pharmaceutical companies towards developing SARS-CoV-2 vaccines, their approvals by the appropriate organizations are now (and rather delayed)

emerging, and vaccination campaigns for mass immunization are just beginning. Therefore, the search for effective antiviral drugs must continue together with the need to contain the spread of the virus by proper everyday preventive actions following the advice provided by the health authorities, which includes social distancing, wearing a mask, and cleaning the hands), and a rational immunomodulatory approach for host immunity-boosting [3-5].

In COVID-19 infection, like other coronavirus infections, SARS-CoV-2 needs to interact with the host cells and replicate its genome [6]. Consequently, virus-host protein-protein interaction (PPI) identification can help us to understand the virus invasion mechanism better and to design proper therapeutic strategies. Experimental and computational studies have revealed PPIs between human targets and SARS-CoV-2 [7, 8] and other viruses [9-11] involved in important host biological processes. Specifically, SARS-CoV-2 interacts with i) innate immune pathways (the interferon and the NF-κB pathway and E3 ubiquitin ligases that regulate antiviral innate immune signaling: TRIM59 and MIB1), ii) bromodomain proteins (BRD2 and BRD4 members of the extra-terminal (BET) domain family of epigenetic readers that bind to acetylated histones to regulate gene transcription), and iii) hijacks ubiquitination pathways for replication and pathogenesis (interacts with members of a cullin-2 RING E3 ligase complex) [7].

In this work, metal-binding molecular targets of COVID-19 infection have been identified by applying a systematic structure-based approach, used previously by our group, to propose putative metalloproteomes in various organisms and viruses [11-13]. Furthermore, possible perturbations in cellular metal homeostasis and molecular linkage between the involved human metalloproteome with several disorders were *in silico* investigated.

2. Methods

All the human targets of SARS-CoV-2 were retrieved from the supplementary material of the study of Gordon *et al.* [7]. The metal-binding proteins were predicted using the strategy applied previously to identify putative metalloproteomes in various organisms [11-15]. The approach combines strategies based on structural data and annotation to identify putative metallo-binders by searching for known metal-binding domains in their sequences [16]. The list of known metal-binding domains has been extracted from the Pfam library (http://pfam.xfam.org/) [17], and the 3D structures of known metalloproteins available from the Protein Data Bank (PDB; http://www.rcsb.org/pdb/) [18] and MetalPDB (https://metalpdb.cerm.unifi.it/) [19]. All the human targets were analyzed for the relevant Pfam metal-binding domains with the search tool HMMER (http://hmmer.org/) [20].

The Centers for Disease Control and Prevention (CDC) provided a list of underlying medical conditions that might increase the risk of severe illness caused by the SARS-CoV-2 virus [2, 21]. All established alleles (at-risk genes) associated with humans disorders were retrieved from the Genome-Wide Association Studies (GWAS) online catalog (https://www.ebi.ac.uk/gwas/) and are shown in **Table** 1. Then, the retrieved genetic loci employed were used to identify gene networks using the random walk algorithm with restart, previously described [11], and the Gene Prioritization and Evidence Collection (GPEC) plug-in of Cytoscape [22]. Using this algorithm, GPEC finds any neighboring interactants of at-risk genes with a topological distance of 1. The genes in the developed networks were defined as the "neighboring genes". Then, each neurological disorder's neighboring genes were individually Venn-analyzed compared to the genes that encode the human targets.

Functional annotation of human targets was performed by the DAVID tool (http://david.abcc.ncifcrf.gov/) [23]. Subcellular localization was predicted based on the UniProt catalog's information (https://www.uniprot.org/) [24]. Their protein abundance information was taken from PaxDb (https.//pax-db.org/) [25].

3. Results

12.3%, 3%, 1.8%, 0.3%, and 0.3% of the studied human proteome interacting with SARS-CoV-2-proteins contained Zn, Mg, Fe, Cu, and Mn metalloproteins, respectively (**Fig. 1**). The complete list of metalloproteins is collected in **Supplementary Table S1** and is illustrated in **Fig. 2**. The majority of these metalloproteins (17%) interact with accessory protein SARS-CoV-2 orf8, and 8.6% interact with structural membrane protein SARS-CoV-2 M and the non-structural proteins SARS-CoV-2 nsp12 and nsp13 (**Table 2**). The majority of the human metalloproteins that interact with the viral proteins of SARS-CoV-2 localized in membranes represent 58.36%, followed by those in the cytoplasm (23.6%), nucleus (8.7%), and mitochondria (0.6%). According to the protein abundance database (paxdb.org), the human Mg-binding targets are abundantly expressed compared with those of Fe-, Mn- Zn-, and Cu-binders (**Fig. 3**). The most significant molecular function gene ontology terms represented in human metalloproteins refer to binding (85%), catalytic (46%), transporter (7%), and transcription (3%) regulator activity. Venn analysis revealed shared genes between human targeted metalloproteome and certain underlying medical conditions that increase the risk for severe illness from the virus that causes COVID-19. These comprise three neurological disorders with Multiple Sclerosis (MS) showing the highest number of shared genes (*MYCBP2, VPS11, CSNK2B,* and *ITGB1*), followed by Parkinson's Diseases (PD) (*CYB5B and RHOA*) and Alzheimer's Disease

(AD) (*RHOA*). Also, two types of cancer were highlighted: Head and Neck Squamous Cell Carcinoma (HNSCC) (*DNMT1*) and Kidney Renal Clear Cell Carcinoma (CCRCC) (*KIRC*). Between other disorders, we found Glaucoma (*SIRT5, RHOA, and LOX*), Age Macular Degeneration (AMD) (*TGB1 and LOX)*, Hypertension (HT) (*ZNF318*), and Smoking (*CYB5B*), as shown in **Table 3**.

4. Discussion

The human metalloproteome targeted by SARS-CoV-2 proteins has been identified from the experimentally supported, high-confidence, SARS-CoV-2 protein–human protein interactions available in the literature [7]. The results show that the content of Zn-binding proteins (12.3%) in the human proteome is significantly higher than that of the other metal ions, followed by the contents of Mg-, Fe-, Cu- and Mn-binding proteins. Based on the present analysis, the metalloproteome has a notable number of zinc transporters [26-31], indicating that the SARS-CoV-2 infection may cause strong intracellular zinc homeostasis disturbances. Additionally, 27% of the zinc-binding domains of the virus targeted human metalloproteome are of the zinc finger-type known by many reports [32-36] to be crucial for the structural stability and catalytic activity of many enzymes [37]. Specifically, four human zinc-binding RING (really Interesting New Gene) E3 ligases can be identified: E3 ubiquitin-protein ligase MIB, MYCBP2, NRDP1, and RBX1. This result is expected since RING E3s are considered acting as hubs in the immunity-regulating network connecting different signaling pathways or different systems [38-40]. One of the Mg-binding proteins is the cation-transporting ATPase 13A3 [41], which is involved in cation transmembrane transfer through channels, indicating that SARS-CoV-2 infection could interfere with metal uptake and efflux, and sensing pathways.

Interestingly, the present study reveals that most metalloproteins identified (17%) interact with the accessory protein SARS-CoV-2 orf8. The orf8 region is poorly conserved among related coronaviruses and is prone to mutations or deletions during interspecies transmission. Although the function of orf8 remains to be elucidated, its structural plasticity and high diversity suggest an important role in SARS-CoV-2 pathogenicity and the virus's ability to spread [42].

This study shows a significant molecular association between certain underlying medical conditions that might increase the risk for severe illness from the virus that causes COVID-19 and the involved human metalloproteome. The zinc-binding proteins show the highest number of shared genes with underlying medical

conditions. Specifically, six Zn-binding proteins are encoded by shared genes with multiple sclerosis, glaucoma, HNSCC, and KIRC cancer types and hypertension:

i) E3 ubiquitin-protein ligase encoded by the *MYCBP2* gene plays a key role in neural development. It is involved in different processes such as regulation of neuronal growth, synaptogenesis, and synaptic plasticity by modulating several signaling pathways, including the p38 MAPK signaling cascade [42].

ii) Vacuolar protein sorting-associated protein 11 homolog (encoded by the *VPS11* gene) plays a role in vesicle-mediated protein trafficking to lysosomal compartments, including the endocytic membrane transport and autophagic pathways [43, 44]. C8.'6C mutation in its RING-H_2 domain causes aberrant ubiquitination and accelerates the turnover of VPS11 protein. Zebrafish harboring a *vps11* mutation with truncated RING-H2 domain demonstrates a significant reduction in central nervous system (CNS) myelination following extensive neuronal death in the hindbrain and midbrain [45].

iii) Casein kinase II subunit beta (encoded by the *CSNK2B* gene) is a ubiquitous protein kinase that regulates metabolic pathways, signal transduction, transcription, translation, and replication. The enzyme is localized at the endoplasmic reticulum and the Golgi apparatus [46]. CK2 is present in high levels in the brain, and mutations encoding the α-subunit of CK2 were previously identified in patients with neurodevelopmental disorders and dysmorphic features [47].

iv) NAD-dependent protein deacetylase sirtuin-5, mitochondrial (encoded by the *SIRT5* gene) activates CPS1 and contributes to the regulation of blood ammonia levels during prolonged fasting: it acts by mediating desuccinylation and deglutarylation of CPS1, thereby increasing CPS1 activity in response to elevated NAD levels during fasting [48, 49]. SIRT5 plays a significant role in inhibiting mitochondrial ROS levels. SIRT5 alleviates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced nigrostriatal dopaminergic degeneration by suppressing mitochondrial-derived ROS levels. Given the crucial roles of mitochondria in neuronal viability, SIRT5 seems well-positioned to suppress the onset and/or pace of neurodegenerative disease [50].

v) DNA methyltransferase 1 (encoded by the *DNMT1* gene) is an enzyme that transfers a methyl group to cytosine nucleotides of genomic DNA. This protein is the major enzyme responsible for maintaining methylation patterns following DNA replication and shows a preference for hemimethylated DNA. DNMTs may be a potential target for enhancing HNSCC chemotherapy by using inhibitors of DNMTs and reversal of gene methylation [51, 52]. It has been reported that DNMT1 enhances the radiosensitivity of neck squamous cell carcinomas via downregulating SMG1 [53].

vi) The zinc finger protein 318 (encoded by the ZNF318 gene) was recognized previously as a blood pressure regulator [54].

The Fe-binding Cytochrome b5 (Cb5) is encoded by the *CYB5B* gene shared with Parkinson's disease and smoking behavior-related traits. This protein is a membrane-bound hemoprotein functioning as an electron carrier for several membrane-bound oxygenases [55]. Cb5 has a high potential as a biomarker of health and disease in the brain because it regulates metabolic pathways essential to maintain normal neuronal function, like lipid biosynthesis, steroid and xenobiotics metabolism, neuronal bioenergetics, and production of reactive oxygen species. Cb5 is highly expressed in pyramidal neurons of the primary and secondary motor areas of the frontoparietal cerebral cortex, hippocampus, vestibular, reticular, and motor nuclei of the cerebellum and brain stem, and also in Purkinje and granule neurons of the cerebellum cortex [56]. Two Mg-binding proteins are encoded by shared genes with Multiple Sclerosis, Alzheimer's Disease, Parkinson's Disease, Glaucoma, and KIRC:

i) integrin beta 1 (encoded by the *ITGB1* gene) is a cell surface receptor associated with integrin alpha 1 and integrin alpha 2 to form integrin complexes that function as collagen receptors [57]. β1 integrin subunit has been implicated in neuronal migration and in the laminar organization of the brain. Formation, maturation, and function of synaptic connections require the engagement of several integrins. Presynaptic β1 integrins serve as counter-receptors for postsynaptic intercellular adhesion molecule-5 (ICAM-5; aka telencephalin) [58]. Integrin beta-1 is mainly expressed in normal cells and in tumor-associated cells, where they control various developing processes, including angiogenesis, tumor progression, apoptosis, and metastasis [59]. Recently, flow cytometry showed that *ITGB1* was expressed at high levels in clear cell renal cell carcinoma [60].

ii) Transforming protein RhoA (encoded *by RHOA gene*) is a small GTPase protein primarily associated with cytoskeleton regulation, mostly actin stress fibers formation and actomyosin contractility [61].

Rho GTPases dysregulated in various neurological diseases/disorders show synaptic irregularity, such as Huntington's Disease, Parkinson's Disease, Amyotrophic Lateral Sclerosis, and Schizophrenia. They are also characterized as key regulators in Alzheimer's disease (AD)-related signals and studied as AD targets [62]. The Cu-binding Protein-lysine 6-oxidase is an enzyme encoded by the *LOX* gene linked to multiple sclerosis and glaucoma. It catalyzes the conversion of lysine molecules into highly reactive aldehydes that form cross-links in extracellular matrix proteins [63]. Localization of *LOX* at the CNS has been reported previously. In these studies, *LOX* is localized at the vascular wall and intracellularly in the brain matrix's cortical and subcortical neurons. Also, *LOX* is one of the genes known to be up-regulated in Amyotrophic Lateral Sclerosis (ALS) patients [64].

5. Conclusions

In this work, the human metalloproteome which is physically associated with SARS-CoV-2 proteins, has been mined from available experimental data and highlighted for the first time. This work strongly indicates the important role of Zn^{2+} in the interplay between COVID-19 and human for two main reasons:

i) The content of Zn-binding proteins (12.3%) is significantly higher than that of the other metal ions.

ii) The Zn-binding proteins have shown the highest number of shared genes with underlying medical conditions that might increase the risk of severe illness from the SARS-CoV-2 virus.

Additionally, most virus-targeted metalloproteins (17%) interact with the accessory protein SARS-CoV-2 orf8, a region with high variability and structural changes related to the virus's ability to spread. Furthermore, PPIs that could cause possible significant perturbation of human zinc homeostasis from viral infection have been identified. Integrated gene network analysis reveals gene circuits shared among the identified metalloproteome and three specific neurological disorders like Multiple Sclerosis, Alzheimer's Disease, Parkinson's Disease, and other specific conditions are known to be implicated in COVID-19 severity such as hypertension and smoking. Bioinorganic chemistry can play an important role in the current pandemic. As pointed out in a recent remarkable report by Kozak, Gray, and Garza-Lopez [65], metal ions might affect the function of structural stability of the SARS-CoV-2

main protease (Mpro). Based on a detailed analysis of Mpro stability, the authors have identified regions where inorganic therapeutic agents could compromise the coronavirus by targeting histidines and/or cysteines. In one scenario, the main protease could be inhibited by Co(III) attachment to His 41, and in another scenario, Co(III) binding to the active-site Cys 145 thiolate would be lethal to enzyme function. Finally, we hope that this study opens the doors for developing metallodrugs as alternatives in the fight against SARS-CoV-2. This is a topic of current intense interest [66, 67], and the well-established abilities of coordination complexes to inhibit different stages of the replicative cycles of several viruses may be a good starting point. Furthermore, we believe that this type of study could be useful for developing more efficient techniques for the reliable detection of SARS-CoV-2, which is also an area of intense research efforts [68-70], in order to control, prevent and therefore reduce its pathogenic spread.

Declaration of Competing of Interest The authors declare no conflict of interest.

Figures

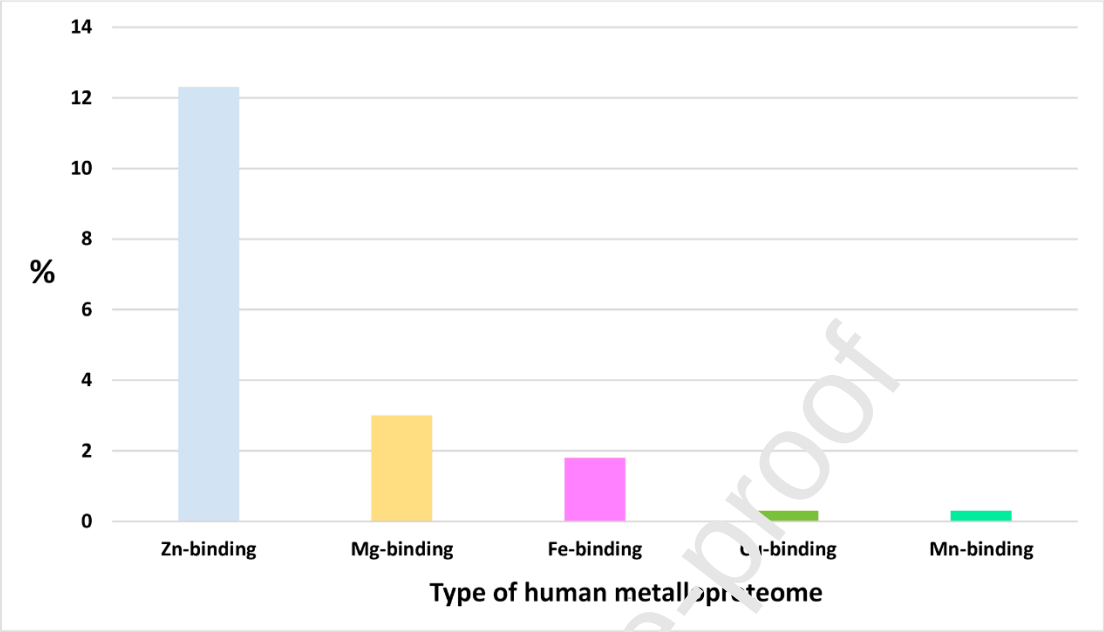

Fig. 1. The content of each type of human metalloproteome that is interacting with SARS-CoV-2-proteins.

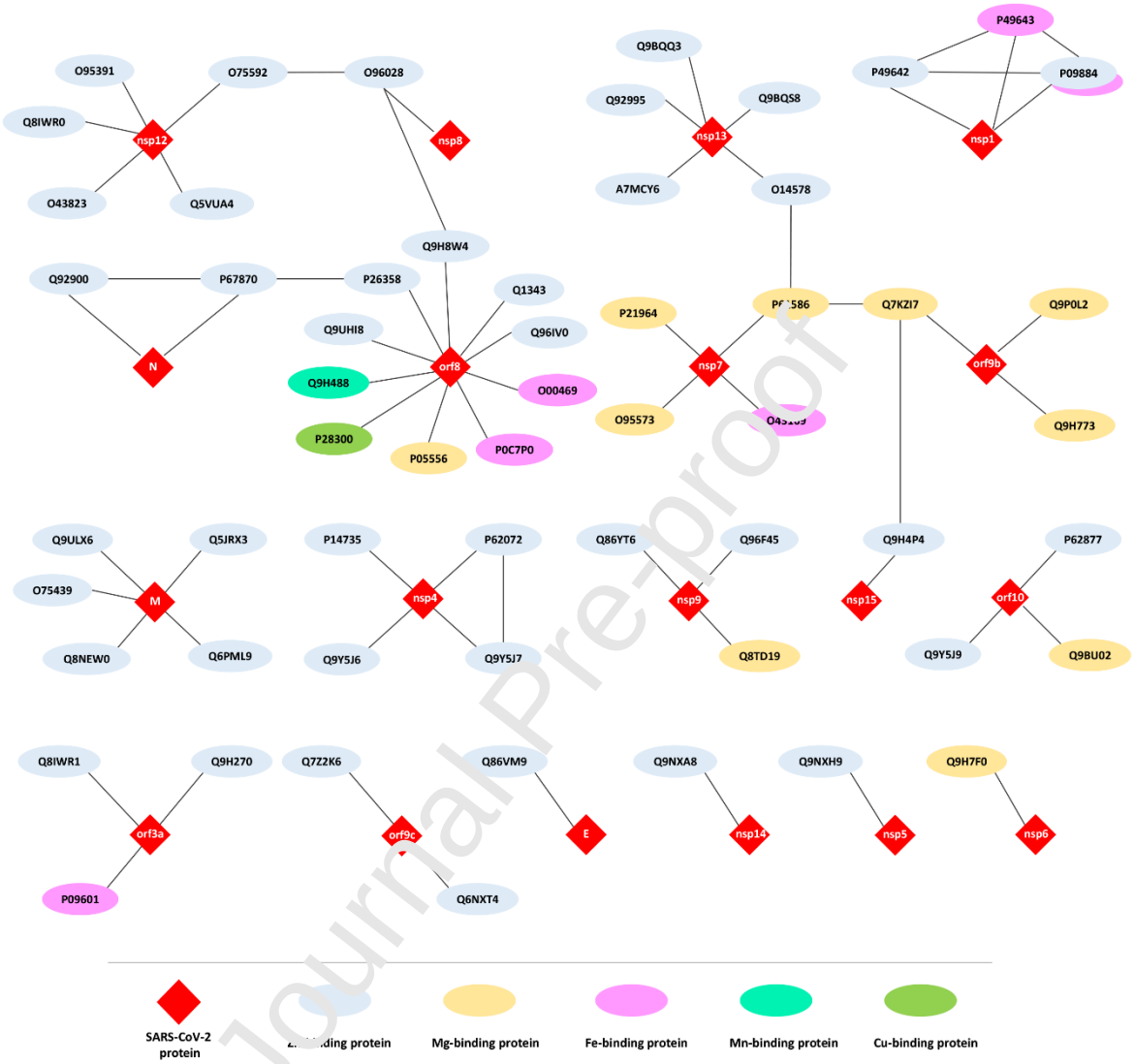

Fig. 2. The PPI interactions between SARS-CoV-2 proteins and human metal-binding proteins (IDs in the nodes correspond to Uniprot protein identifiers).

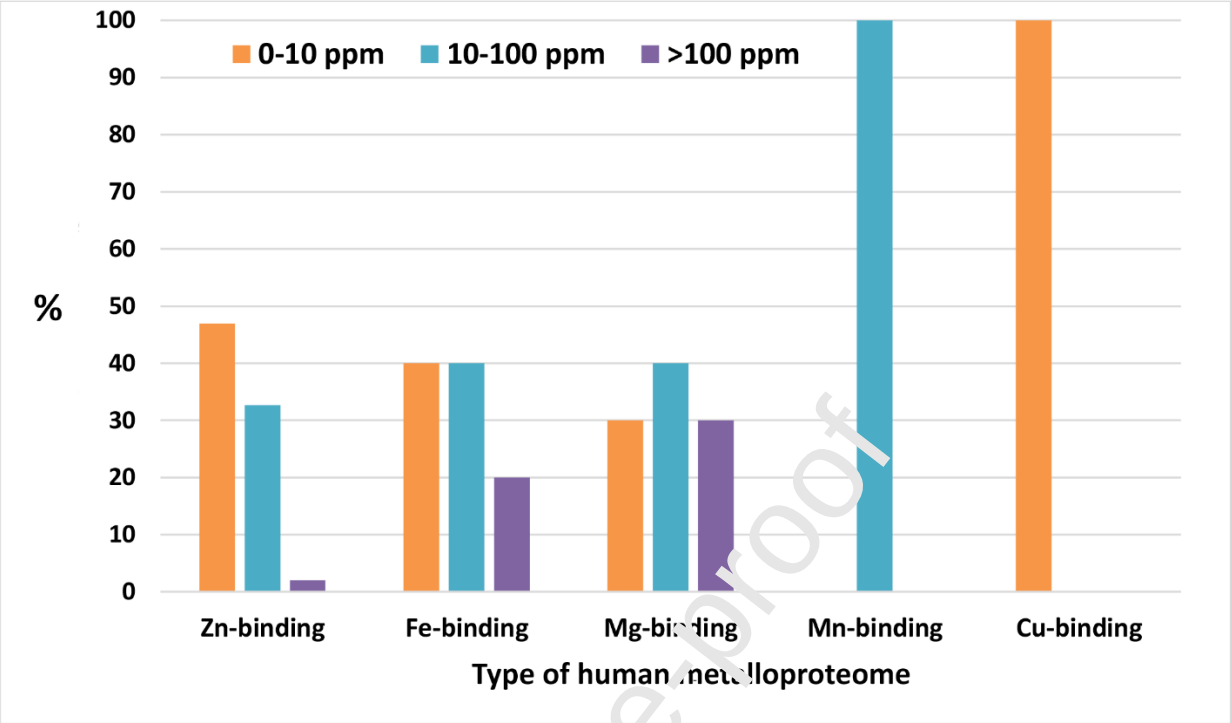

Fig. 3. The protein abundance of target-metalloproteins

Tables

Table 1 Humans disorders or conditions retrieved from the Genome-Wide Association Studies (GWAS) online catalog.

	Diseases/disorders
Neurology	Alzheimer's Disease, Parkinson's Disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, Vascular Dementia, Restless Leg Syndrome, Migraine, Creutzfeldt—Jakob Disease, Narcolepsy, Autism-Autism Spectrum
Oncology	Urothelial Bladder Carcinoma, Breast Cancer, Colorectal Adenocarcinoma, Glioblastoma, Head and Neck Squamous Cell Carcinoma, Kidney Cancer, Acute Myeloid Leukemia, Lung Adenocarcinoma, Lung Squamous Cell Carcinoma, Ovarian Cancer, Uterine Corpus Endometrial Carcinoma, Multiple Myeloma
Ophthalmology	Age Macular Degeneration, Glaucoma
Cardiology	Hypertension, Heart Failure
Endocrinology	Diabetes, Obesity
Pulmonology	Chronic Obstruct Pulmonary, Lung Cystic Fibrosis, Pulmonary Fibrosis, Asthma, Smoking
Nephrology	Chronic Kidney
Hematology	Thalassemia, Sickle Cell Anemia
Obstetrics	Pregnancy

Table 2 Distribution of the metallo-binding interactors of SARS-CoV-2 proteins.

SARS-CoV-2 protein	Number of target-metalloproteins
SARS-CoV-2 orf8	10
SARS-CoV-2 M	5
SARS-CoV-2 nsp12	5
SARS-CoV-2 nsp13	5
SARS-CoV-2 nsp4	4
SARS-CoV-2 nsp7	4
SARS-CoV-2 nsp1	3
SARS-CoV-2 nsp9	3
SARS-CoV-2 orf10	3
SARS-CoV-2 orf3a	3
SARS-CoV-2 orf9b	3
SARS-CoV-2 N	2
SARS-CoV-2 orf9c	2
SARS-CoV-2 E	1
SARS-CoV-2 nsp14	1
SARS-CoV-2 nsp15	1
SARS-CoV-2 nsp5	1
SARS-CoV-2 nsp6	1
SARS-CoV-2 nsp8	1

Table 3 Shared genes between human metalloproteome targeted by SARS-CoV-2 proteins and associated disorders.

	Neurological disorders			*Cancer*		*Others*			
Proteins	**Multiple Sclerosis**	**Alzheimer's**	**Parkinson's**	**Head and Neck Squamous Cell Carcinoma**	**Kidney Renal Clear Cell Carcinoma**	**Age Macular**	**Glaucoma**	**Hypertension**	**Smoking**
Zn-binding	MYCBP2,VPS11,CSNK2B			DNMT1			SIRT5	ZNF318	
Fe-binding			CYB5B						CYB5B
Mg-binding	ITGB1	RHOA	RHOA		ITGB1	ITGB1	RHOA		
Mn-binding									
Cu-binding						LOX	LOX		

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January 06, 2021

I would like to state that there are no conflict of interest.

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Highlights

- 58 human metalloproteins were identified as targets of SARS-CoV-2.
- The most infected metalloproteins are Zn-binding proteins.
- The most infected metalloproteins interact with SARS-CoV2 orf8 protein.
- Shared genes among infected Zn-proteome and human disorders were found
- These molecular linkage might increase the risk of severe COVID-19

January 06, 2021

I would like to state that there are no conflicts of interest and all authors approved the final manuscript.

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The identified human metalloproteome targeted by SARS-CoV-2. Zn-binding proteins are most affected and their main interactor is the viral orf8 protein, whose antibodies are one of the principal markers of SARS-CoV-2 infections. A molecular linkage has been identified between the involved human metalloproteome with underlying medical conditions.