Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Where all the Roads Meet? A Crossover Perspective on Host Factors Regulating SARS-CoV-2 infection

Sneh Lata1†, Ritu Mishra1†, Ravi P. Arya2†, Pooja Arora3†, Anismrita Lahon4†, Akhil C. Banerjea4* and Vikas Sood5*

1 - Virology Laboratory, National Institute of Immunology, New Delhi, India
2 - KSBS, Indian Institute of Technology, New Delhi, India
3 - Hansraj College, University of Delhi, New Delhi, India
4 - Institute of Advanced Virology, Kerala, India
5 - Biochemistry Department, Jamia Hamdard, New Delhi, India

Correspondence to Akhil C. Banerjea and Vikas Sood: akhil@nii.ac.in (A.C. Banerjea), v.sood@jamiahamdard.ac.in, vikas1101@gmail.com (V. Sood), snehl5555 (S. Lata), RITUMI74552090 (R. Mishra), Raviarya08 (R.P. Arya), anismrita (A. Lahon), sys_bio (V. Sood)

https://doi.org/10.1016/j.jmb.2021.167403
Edited by M.F. Summers

Abstract

COVID-19 caused by SARS-CoV-2 is the latest pandemic which has thrown the world into an unprecedented social and economic uncertainties along with huge loss to humanity. Identification of the host factors regulating the replication of SARS-CoV-2 in human host may help in the development of novel anti-viral therapies to combat the viral infection and spread. Recently, some research groups used genome-wide CRISPR/Cas9 screening to identify the host factors critical for the SARS-CoV-2 replication and infection. A comparative analysis of these significant host factors (p < 0.05) identified fifteen proteins common in these studies. Apart from ACE2 (receptor for SARS-CoV-2 attachment), other common host factors were CSNK2B, GDI2, SLC35B2, DDX51, VPS26A, ARPP-19, C1QTNF7, ALG6, LIMA1, COG3, COG8, BCOR, LRRN2 and TLR9. Additionally, viral interactome of these host factors revealed that many of them were associated with several SARS-CoV-2 proteins as well. Interestingly, some of these host factors have already been shown to be critical for the pathogenesis of other viruses suggesting their crucial role in virus-host interactions. Here, we review the functions of these host factors and their role in other diseases with special emphasis on viral diseases.

Introduction

Since the beginning of COVID-19 (coronavirus disease 19) pandemic last year; identification of anti-viral genes and host-factors has become the central focus of the biomedical research fraternity. Since its discovery, genome-wide CRISPR/Cas9 based screening has been contributory in identification of novel druggable host factors against pathogens. Diverse and comprehensive screening results were published recently from different research groups to identify the most potent and significant genetic factors needed for SARS-CoV-2 replication and infection.1–4 These groups have generated cell lines transfected with libraries of small guide (sg) RNA in a way that only one gene is modified or deleted per cell. These genome-scale screening studies have targeted several genes in the human genome by using different CRISPR-Cas9 libraries. Using robust-rank aggregation (RRA) on the guide relative enrichment, authors have identified the genes which had significant RRA enrichment showing p-value < 0.05.1–4 Interestingly, they also
used different doses of SARS-CoV-2 viruses at MOI 0.01 and 0.3 to identify host factors involved in entry, replication and pathogenesis of the virus. The authors observed that there is a high degree of shared genes which are perturbed in both the conditions. This also shows that several common genes are involved in viral pathogenesis irrespective of the concentration of the virus used to infect the cells. The authors characterized the genes thus identified as pro-viral or anti-viral in nature. Some key genes found significantly critical for successful viral life cycle were ARID1, KDM6A, JMD6, SMARCC1, and CTSL (assisted in the entry of all corona viruses); SWI/SNF remodelling complex, histone-modifying enzymes, Runx3 dependent CDKN1A transcription regulatory molecules, CTSL associated cystatin and endo-lysosome lumen gene sets, endosomal protein sorting Retromer complex: VPS26A, VPS29, VPS35, and SNX27 and endosomal trafficking Commandeer complex: COMMD2, COMMD3, COMMD3-BM11, and COMMD4; vacuolar-ATPase proton pump: ATP6AP1, ATP6AP2, ATP6V0B, ATP6V0C, ATP6V0D1, ATP6V1A (involved in cholesterol metabolism), host factors involved in pathways related to heparan sulphate biosynthesis and transport (such as EXT1, EXT2, EXT3, B3GALT6, B3GAT3, B4GALT7, SLC35B2, XYL2, HS2ST1 and NDST1), regulation of intracellular protein trafficking, processing, and sorting through the conserved oligomeric Golgi (COG) complex (including COG2, COG3, COG4, COG7, and COG8); and 3 members of the PI3K pathway: PIK3C3/PS34, WDR81, and ACP5 (involved in phosphatidylinositol biosynthetic processes). The genes involved in Nucleosome Remodeling Factor (NURF) complex were identified as anti-viral factors for corona viruses. Endoplasmic reticulum membrane protein complex (EMC), the DEAH-box helicases DHX36 and DHX38, factors from Golgi family (GOLGA6L1 and GOLGA8O), the general transcription factor IIIC subunits (GTF3C5 and GTF3C6), the tRNA methyltransferases (TRMT5 and TRMT6), the G-protein-coupled receptors (GPR89A and GPR89B), the transmembrane p24-trafficking proteins (TMED2 and TMED10) and genes involved in phosphatidyethanolamine biosynthesis (PCYT2 and EPT) were also found to be interacting with SARS-CoV-2 as identified in the screen. These identified genes were further investigated for their interaction with SARS-CoV-2 proteins. The analysis revealed that many of these host factors had direct protein–protein interactions with the viral proteins.

Though these studies provided valuable insight into various host factors critical for SARS-CoV-2 infection, comparative analysis of the data might shed light on the host factors that are extremely critical for viral replication. In order to identify common candidates regulating SARS-CoV-2, highly significant host factors (p < 0.05) were selected from each study and compared for identification of common host factors. The analysis decoded that ACE2 was the only candidate that was common in the gene pool from all the four studies. Further analysis identified 14 more candidates that were common in at least three out of the four studies which we elucidate in this present work. The candidate genes other than ACE2, common from these studies were entailed in several cellular processes including Golgi homeostasis (Component of Oligomeric Golgi Complex 3 (COG3) and Component of Oligomeric Golgi Complex 8 (COG8)), vesicular trafficking (GD dissociation inhibitor 2 (GDI2)), regulation of mitosis (cAMP regulated phosphoprotein-19 (ARPP-19)), sulphation of biomolecules in endoplasmic reticulum and Golgi bodies (solute carrier family 35 member B2 (SLC35B2)), actin binding protein (LIM domain and actin binding 1 (LIMA1)), innate immune pathways (Toll-like receptor 9 (TLR9)), protein transfer from endosomes to Golgi bodies (retromer complex component A (VPS26A)), protein kinase involved in cell metabolism (casein kinase 2 beta (CSNK2B)), signal transduction receptors (Leucine-rich repeat neuronal 2 (LRRN2)), cell cycle progression (DEAD box helicase 51 (DDX51)), glucosyltransferase family member (alpha 1–3 glucosyl transferase (ALG6)), transcriptional corepressor (BCL6 corepressor (BCOR)) and C1q and TNF related 7 (C1QTNF7). We selected these proteins for further elaborated discussion, specially focusing on their role in the pathogenesis of various other viruses.

**ACE2**

Angiotensin-converting enzyme 2 (ACE2) is an important component of RAS (renin-angiotensin system) signaling pathway. This pathway regulates homeostasis of vascular function like blood pressure, natriuresis and blood volume control. ACE2 is a single pass type-1 membrane protein. It is a zinc containing metalloenzyme having carboxypeptidase activity attached to the cell membranes of cells located in the lungs, arteries, heart, kidney, and intestines. It lowers the blood pressure by catalysing the hydrolysis of angiotensin II into angiotensin 1–7.

Being a transmembrane protein, ACE2 has been identified to serve as the entry point into the host cells for coronaviruses HCoV-NL63, SARS-CoV-9,10 and SARS-CoV-2 (the virus that causes COVID-19). The spike protein of these coronaviruses interacts with enzymatic domain of ACE2 on the surface of cells which results in the endocytosis and translocation of the virus into the host cell.13,14 This process requires the cleavage of spike protein by cellular serine protease Transmembrane Protease Serine 2 (TMPRSS2). The interaction of ACE2 and spike protein of coronaviruses reduces the levels of ACE2 due to its
internalization and degradation in the endosomes which may result in the lung damage.\textsuperscript{20,21} The acute lung injury induced by SARS-CoV infection has been found to be attenuated in ACE2 knockout mice compared with wild-type mice.\textsuperscript{9}

Similar mechanisms have been proposed for the severe lung injury induced by avian influenza A viruses H5N1, H7N9 and swine influenza virus H1N1 also, which were spread worldwide in humans with a high mortality rate. It has been reported that ACE2 expression is downregulated in the lungs of mice after virus infection. The knock-out of ACE2 in infected mice aggravates the lung injury while the administration of recombinant ACE2 protein amends virus induced lung injury in mice.\textsuperscript{22–24} ACE2 has also been found to protect against the severe lung injury induced by Respiratory Syncytial Virus (RSV) and knock-out of ACE2 aggravates RSV associated lung disease pointing towards the critical role of ACE-2 in respiratory viruses.\textsuperscript{25}

\section*{CSNK2B}

Casein kinase 2 subunit beta (CSNK2B) is the beta subunit of casein kinase 2 (CSNK2) protein. CSNK2B has been found to be located in the cellular endoplasmic reticulum and Golgi apparatus. It phosphorylates its target proteins at serine or threonine residues. This enzyme is a tetramer of two \(\alpha\) and two \(\beta\) subunits. Different species may have two related forms of alpha subunits i.e. \(\alpha\) and \(\alpha'\) or two related forms of beta subunits i.e. \(\beta\) and \(\beta'\). CSNK2 alpha subunits are the catalytic subunits having serine/threonine kinase activity. CSNK2 beta subunits are the regulatory subunits having an N-terminal auto-phosphorylation site, an internal acidic domain and a potential metal binding motif. CSNK2 is a well conserved protein kinase which is ubiquitously expressed and has been found to be important for cell metabolism, proliferation, differentiation, signal transduction and survival.\textsuperscript{26} De novo variation in CSNK2B gene has been found to be associated with epilepsy, intellectual disability (ID) and developmental delay. The zinc binding domain of the protein was observed to be the hot-spot for mutation.\textsuperscript{27,28} CSNK2B knockout mice have been found to be embryonically lethal.\textsuperscript{29}

CSNK2B has been recently found to interact with N protein of SARS-CoV-2 and is critical for viral infection.\textsuperscript{1–4,9} Recent proteomics based studies also identified CSNK2B as one of the interacting partners during Zika virus and SARS-CoV-2 infections.\textsuperscript{30,31} It has been reported to be essential for the infection of several other viruses also. Inhibition of CSNK2B led to the increased H1N1 entry and replication.\textsuperscript{32} Inhibition of CSNK2 impaired Vaccinia virus (VACV) dissemination and actin tail formation.\textsuperscript{33} CSNK2 catalytic activity has also been found to be required for the replication of different HPV (Human Papilloma Virus) types and its inhibition by CX4945, an ATP-competitive small molecule inhibitor of CSNK2 suppresses the viral replication by regulating stability and nuclear retention of E1 protein.\textsuperscript{34} CSNK2 has been reported to phosphorylate many HIV-1 (Human Immunodeficiency Virus 1) proteins such as Rev,\textsuperscript{35–39} Vpu,\textsuperscript{40–44} Matrix,\textsuperscript{45} protease\textsuperscript{46} and reverse transcriptase\textsuperscript{47–50} leading to enhanced HIV-1 replication. CSNK2 has also been found to phosphorylate immediate early protein IE63 of Herpes Simplex Virus-1 (HSV-1) and regulate virus replication.\textsuperscript{51} The association of CSNK2B with various diverse viruses further point towards its critical role in SARS-CoV-2 viral biology.

\section*{GDI2}

GDP dissociation inhibitor beta (GDI2) regulates the GDP-GTP exchange reaction of members of the Rab family proteins which are small GTP-binding proteins of the Ras superfamily involved in vesicular trafficking of molecules between cellular organelles. It slows down the rate of dissociation of GDP from Rab proteins and releases GDP from membrane-bound Rabs. GDI2 is ubiquitously expressed. The GDI2 gene contains many repetitive elements indicating that it may be prone to inversion/deletion rearrangements. GDI2 has recently been identified as a host factor crucial for SARS-CoV-2 replication in multiple CRISPR-based screening studies. GDI2 was also shown to interact with M, NSP4, NSP6, ORF3B and ORF7B proteins of SARS-CoV-2.\textsuperscript{1–4,52}

GDI2 has been found to play important role in the life cycle of several other viruses too. GDI2 has been shown to be an important regulator of Influenza A virus (IAV) replication.\textsuperscript{53–55} GDI2 was also shown to be associated with Tobacco Mosaic Virus (TMV) 126 kDa replication protein which affects the vesicular trafficking and enhances the establishment of TMV infection.\textsuperscript{56} GDI2 was also found to be associated with Vesicular Somatitis Virus (VSV) virions.\textsuperscript{57} GDI2 was also reported to be associated with Chikungunya Virus (CHIKV) infection.\textsuperscript{58} It was also found to be differentially regulated in avian influenza infected chicken embryo fibroblasts.\textsuperscript{59} The expression of GDI2 was observed to be up-regulated during Zika virus (ZIKV) infection.\textsuperscript{60} Interestingly, a recent deep learning based study identified GDI2 among top 10 host factors that could be modulated to inhibit coronaviridae family viruses.\textsuperscript{61}

\section*{SLC35B2}

SLC35B2 is a solute carrier family 35 member B2 gene, encoding 3'-phosphoadenosine 5'-phosphosulfate (PAPS) transporter 1 (PAPST1) protein.\textsuperscript{62} This protein is involved in Heparan Sulphate proteoglycan synthesis and thus play a critical role in viral attachment to host cells and viral
SLC35B2 has strongly emerged as a host factor crucial for SARS-CoV-2 replication in recent multiple CRISPR-based screenings. It also interacts with S, M, NSP4, NSP5, NSP6, NSP13, NSP14, ORF3A, ORF7A and ORF7B proteins of SARS-CoV-2.1–4,52 These observations suggest that SLC35B2 might be playing a determining role in coronavirus replication and life cycle as well, which should be further investigated. One recent study has highlighted that cellular heparan sulphate is essential for efficient SARS-CoV-2 infection process,64 thus suggesting its critical impact on viral replication and viral load in newly infected cells.

The role of SLC35B2 in viral life cycle has also been studied with ZIKV virus, DENV (Dengue Virus) and many other viruses. In a knockout study of SLC35B2, it was found that entry process of ZIKV virus is not reduced but DENV virus attachment was impacted.65 However, in this same study, it was observed that heparan sulphate is involved in the ZIKV replication and induces apoptosis in host cells. A genome-wide CRISPR-Cas9 screening again identified PAPST1 (sulfotransferase enzyme coded by SLC35B2) as a host entry factor for Schmallenberg virus (SBV) which is a vector-borne Orthobunyavirus known to cause abortions and congenital malformations in juvenile ruminants. The other viruses of bunyaviruses family which is an apoptotic anti-cancer gene, therefore established their role as negative regulator of p53, intrinsic apoptotic pathway regulation. A study has highlighted that cellular heparan sulphate in coronavirus replication and life cycle as well, that SLC35B2 might be playing a determining role in CRISPR-Cas9 based screenings. It also interacts with S, M, NS, NSP4, NSP5, NSP6, NSP13, ORF3A, ORF7A, ORF7B, ORF6 and ORF8 proteins of the virus.1–4,53 The interaction of VPS26A with multiple SARS-CoV-2 protein points towards its critical role in virus biology.

DDX51

DDX51 belongs to the DEAD-box RNA helicase (DDX) family which are ubiquitously expressed in almost all cells and are known to participate in RNA metabolism, RNA splicing, translation, pre-rRNA processing as well as ribosome assembly.68,70 They were reported to play a role in intrinsic apoptotic pathway regulation. A study has established their role as negative regulator of p53, which is an apoptotic anti-cancer gene, therefore actively promote cell proliferation.71,72

Specific role of DDX51 on SARS-CoV-2 replication still needs to be unearthed, however, it has been recently identified as one of the host factors crucial for the replication of SARS-CoV-2 in CRISPR-Cas9 based screenings. It also interacts with NSP6 and ORF14 proteins of SARS-CoV-2.1–4,52 A latest review on the comprehensive role of DEAD-box (DDX) RNA helicases have been published by Squeglia et al. where it has been discussed that how DDX proteins are hijacked by coronaviruses and redirected to participate in crucial DDX-mediated viral replication steps.73 Based on above trends it can be proposed the emergence of DDX51 in SARS-CoV-2 virus - host interaction screenings indicates a unique and novel role which DDX51 might be playing. One CRISPR-based study to generate the virus-host interaction network for Respiratory syncytial virus (RSV) has also reported DDX51 as a host factor but their detailed molecular mechanism has not been investigated yet.74

VPS26A

VPS26A is a member protein of a large multimeric complex (retromer complex) required for retrograde transport of cellular proteins from endosomes back to trans-Golgi network. There are many other genes such as VPS35, VPS29, VPS5, Vps17 and VPS26 etc. known as vacuolar protein sorting (VPS) genes.75 These proteins basically act as coat proteins for the vesicles budding out of endosomes and are also known to be playing certain roles in cargo sorting at endosomal membrane.75 Their roles have been widely studied such as in Drosophila oogenesis; they are known to mediate Notch signalling.76 In many neurological diseases such as Alzheimer’s, Parkinson’s disease and others, VPS complex is known to be perturbed. It is known that VPS35 which is a scaffold protein interacts with VPS26 and VPS29. This trimer complex then plays an important role in endosomal trafficking pathway. Researchers have also identified that various combinations of these retromer components exhibit differential impact in neuroblastoma cells.76

Being a member protein of a cellular housekeeping pathway such as endosomal trafficking, VPS protein certainly becomes a favourite target of viruses when it comes to support their own replication and budding. CRISPR-based screening of host factors needed for SARS-CoV-2 replication has also shown VPS26A protein as a common emerging host factor. VPS26A also interacts with S, M, E, NSP4, NSP5, NSP6, NSP13, ORF3A, ORF3B, ORF7A, ORF7B, ORF6 and ORF8 proteins of the virus.1–4,53 The interaction of VPS26A with multiple SARS-CoV-2 protein points towards its critical role in virus biology.

It will be interesting to know the exact role that these VPS family member proteins might be playing in SARS-CoV-2 pathogenesis. Till date, however no reports have surfaced to demonstrate the specific influence of VPS26A on SARS-CoV-2 replication, though the role of VPS family members has previously been investigated in the pathogenesis of several other viruses. Role of VPS35 is reported during HCV (Hepatitis C virus) viral life cycle. HCV NS5 interacts with VPS35 at replication sites. This indicates that these retromer protein complexes have a specific role to play
ARPP-19

Cyclic adenosine monophosphate-regulated phosphoprotein-19 (ARPP-19) was first identified in bovine brain as a substrate for cAMP-dependent protein kinase (PKA). In the brain region, ARPP-19 was shown to mediate the effect of nerve growth factor in axon growth and synaptic plasticity via increasing the stability of Growth associated protein 43 (GAP 43) mRNA. Decreased levels of ARPP-19 have been associated with pathogenesis of Down syndrome and Alzheimer’s disease. ARPP-19 has been shown to play a vital role in mitosis regulation in the cell. On getting phosphorylated by protein kinase Gwalt (Gwl) at serine or by cyclin B-Cdk1 at different site in Gwl-independent manner, it inhibits protein phosphatase 2A (PP2A) and mediates smooth transition of the cell from G2 to M phase. Based on sequence homology, it was found to be similar to alpha-endosulfine (ENSA) which also binds and inhibits PP2A inhibition and play an important role in cellular mitosis. Though extensive studies suggest the role of ARPP-19 in cancer progression, however, its involvement in viral infections came to our knowledge recently when it was shown to be an important factor for SARS-CoV-2 infection. Extensive literature survey failed to identify any report where the role of ARPP-19 was studied with respect to viral pathogenesis. Therefore, identification of ARPP-19 as an essential factor for SARS-CoV-2 replication have opened new avenues where the role of this host factor in viral pathogenesis can be studied.

C1QTNF7

C1q and tumour necrosis factor-related protein 7 (C1QTNF7), also known as C1q complement/TNF-related protein 7 (CTRP7) is a secreted protein that belongs to a family of adiponectin paralogs known as C1q complement/TNF-related protein (CTRP), which has a C-terminal globular C1q-like domain. It is highly expressed in the adrenal glands, in peri-adrenal adipose tissue and lung. Studies conducted with a knock-out mouse model for CTRP7 suggested a physiological role of CTRP7 in decreased glucose metabolism, increased inflammation and liver fibrosis linked with obesity. The genome-wide association study has found several single nucleotide polymorphisms (SNPs) in CTRP7 gene associated with conduct disorder symptomatology which is one of the widespread childhood psychiatric disorder. Recently, CTRP7 has been suggested as one of the markers for coronary artery disease.

The role of C1QTNF7 in viral infections has not been much explored. A single study has shown C1QTNF7 to be dysregulated in the lungs of mice infected with influenza virus. It was recently reported to play an important role in SARS-CoV-2 pathogenesis, however the exact role of C1QTNF7 in SARS-CoV-2 replication has not been deciphered yet.

ALG6

Alpha-1,3-glucosyltransferase (ALG6) gene encodes for the enzyme alpha 1,3-glucosyltransferase that belongs to a family of glucosyltransferases. The enzyme enables the transfer of glucose to the lipid-linked growing oligosaccharide that is important for N-linked glycosylation of protein and fats. The mutation of human ALG6 leads to Carbohydrate-Deficient Glycoprotein Syndrome (CDGS) type-1c which affects many parts of the body including brain, eyes, liver and endocrine system. The syndrome is grouped under congenital disorder of N-linked glycosylation type 1C (CDG1C). Females with the syndrome demonstrated poor production of sex hormones resulting in delayed puberty. Although C998T resulting in an A333V substitution is the most frequent disease-causing mutation in ALG6 gene that leads to enzyme with reduced activity, the gene may harbour multi-allelic mutation within it. Since glycosylation plays a very important role in expression and functioning of proteins, a single nucleotide polymorphism in ALG6 gene has been associated with survival of cutaneous melanoma patients.

Literature survey revealed that presently there are no studies related to the role of ALG6 in viral biology. However, recent CRISPR/Cas screens identified this host factor as critical for the pathogenesis of SARS-CoV-2. ALG6 was also found to be associated with several SARS-CoV-2 proteins including ORF7a, ORF7b, ORF8, M and E proteins. Association of ALG6 with SARS-CoV-2 in multiple studies further points towards critical role in SARS-CoV-2 infection.
LIMA-1

LIM domain and actin-binding-1 (LIMA-1) gene encodes for a protein named as epithelial protein lost in neoplasm (EPLIN) or sterol regulatory element binding protein 3 (SREBP3) that was first identified as a cytoskeletal protein expressed in human epithelial cells. It has a 54-residue centrally-located ln-11, isl-1, and mec-3 (LIM) domain that allows it to interact with several proteins. Majority of human epithelial cancer cell lines and cancers including breast, prostate and oesophageal show nil or very low expression of EPLIN/LIMA-1. Song et al. showed its role in the inhibition of anchorage independent-growth of some transformed cells owing to its association and regulation of actin cytoskeleton. It has been shown to play a crucial role in actin dynamics via linking cadherin-catenin complex to F-actin and stabilizing actin filaments. Ohashi et al. found that pS3 mediates inhibition of cancerous cell invasion via LIMA-1 and considered LIMA-1 as one of the novel prognostic predictors for tumour inhibition which has a potential in tumour suppression. In humans, one of the LIMA-1 variant has been shown to decrease absorption of intestinal cholesterol, thus lowering low-density lipoprotein cholesterol. In fact, it is considered as one of the factors to control hypercholesterolemia. Recent CRISPR-Cas9 based screenings have found LIMA-1 to be crucial for SARS-CoV-2 infection. It has also been shown to be associated with SARS-CoV-2 receptor ACE2 thereby suggesting its possible role in viral entry. There are no reports showing the importance of LIMA-1 in other viral infections till now.

COG3 and COG8

The Conserved Oligomeric Golgi (COG) complex is a hetero-octameric complex made up of eight proteins (COG1 to COG8) and plays central role in Golgi trafficking, maintenance of Golgi structure and integrity, and management of the distribution of glycosylation enzymes. Biochemical and structural analysis revealed that these proteins are organized into two sub-complexes or lobes; lobe A (COG1, COG2, COG3 and COG4) and lobe B (COG5, COG6, COG7 and COG8) and these two lobes connected through interactions between COG1 and 8. Mutations in these COG proteins have been detected in patients with congenital disorders of glycosylation (CDG) of variable severity. Though these proteins are well characterized, their role in viral infections is poorly understood. Recently, COG3 and COG8 were found to play important role in SARS-CoV-2 infection and replication. Recent proteomics results also revealed that COG3 interacts with ORF3B, ORF6, ORF7A and ORF7B proteins of SARS-CoV-2. Lobe B component COG8 was also shown to interact with NSP14 protein of SARS-CoV-2 which plays important role in viral replication and transcription. This viral protein functions as a proofreading exo-ribonuclease and also as methyl transferase for viral mRNA capping. Interaction of NSP14 with COG proteins suggests the role of COG proteins in SARS-CoV-2 virus replication but its exact mechanism is not yet deciphered.

There are few reports suggesting the role of COG proteins in the replication of other viruses also. COG complex proteins have been reported to facilitate orthopoxvirus entry, fusion and spread. Experiments using cell lines with individual COG gene knockout (KO) mutations revealed that COG3 and COG6 KO cells significantly reduce vaccinia virus entry. COG3 has been also identified as a crucial host factor important for extracellular vaccinia virus release and spread/distribution. RNAi-mediated silencing of all lobe B components of the COG complex (COG5, COG6, COG7 or COG8) has been reported to impair HIV-1 replication in P4R5 MAJl cells. CRISPR-CAS9 based screening also revealed that uptake of Sindbis Virus and dsRNA depends upon the heparan sulphate pathway and the expression of COG3, COG4 and COG8 proteins. Among COG3, COG4 and COG8 proteins, COG3 and COG4 were involved in dsRNA induced cell death. Another study utilizing haploid genetic screen further confirmed the involvement of all COG molecules (except that of COG6) in Rift Valley Fever Virus infection. The appearance of these protein in several screens involving viral infections further points towards their important role in viral biology.

BCOR

BCL6 interacting co-repressor (BCOR) is a ~180 kDa nuclear protein expressed ubiquitously in human tissues. BCOR was identified as the co-repressor involved in BCL6 repression. BCOR has two functional domains: the BCL6-binding domain that interacts specifically with the transcriptional repressor BCL6 and PUF3 domain that mainly interact with proteins involved in histone regulation. BCL6 has important role in T cell function. Increased expression of BCL6 in follicular helper T cells promotes B cells to generate distinct and very specific antibodies. BCOR has been reported for the interaction with histone deacetylases (HDACs) and also engages in macro-molecular complexes for epigenetic modifications to direct gene silencing.

The role of BCOR in viral pathogenesis has not been well studied yet. Epstein–Barr virus (EBV) induced gastric carcinomas have shown high involvement of mutations in BCRO genes. Recent CRISPR-CAS9 based screenings showed that BCOR is required for SARS-CoV-2 pathogenesis. Recently, BCOR has also been involved in the replication of SARS-CoV-2.
found to interact with NSP7 and NSP16 proteins of SARS-CoV-2 which are required for the virus replication complex formation. Interaction of BCOR with these replication accessory proteins may support the virus replication but this needs to be further investigated to know the exact mechanism.

### LRRN2

Leucine-rich repeat neuronal protein 2 (LRRN2) belongs to the leucine-rich repeat superfamily encoded by the LRRN2 gene. This protein (~79 kDa) has been identified to be overexpressed in malignant gliomas and its function may be related to cell-adhesion or signal transduction. The same protein has also been designated as GAC1 (glioblastoma amplification on chromosome 1). Not much is known about its role in viral pathogenesis. LRRN2 has been reported to be important for the pathogenesis of SARS-CoV-2. LRRN2 has also been recently reported to interact with ORF3A and ORF7B proteins of SARS-CoV-2 which have been involved in virus replication and virion assembly. The novel interaction of LRRN2 with SARS-CoV-2 proteins may suggest its role in the SARS-CoV-2 pathogenesis. Given the fact that this host factor has not been studied in detail till now, its association with SARS-CoV-2 biology might fuel its research in the field of virology that might lead to identification of novel cellular pathways that viruses might utilize for successful replication in the host cells.

### TLR9

Toll-like receptors (TLRs) are key molecules of innate immune system and members of pattern recognition receptors (PRRs) family. In mammals, 12 types of TLRs have been detected in various cells. Upon activation, these TLRs stimulate variety of inflammatory cytokines and interferons. TLR9 recognizes unmethylated cytosine-phosphate-guanine (CpG) dinucleotides, commonly found in bacterial and viral DNA and triggers different downstream signalling molecules to produce inflammatory cytokines and interferons. The expression of TLR9 has been observed in variety of cells i.e. plasmacytoid dendritic cells, macrophages, monocytes and B lymphocytes. Apart from bacterial or viral infections, TLR9 is activated in several other conditions like auto-immune disease, cancer and tissue damage. TLR9 is not only activated during infection with bacteria and DNA viruses, RNA viruses such as influenza or dengue virus also activates TLR9 expression. The activation of TLR9 during RNA virus infection might be due to release of mitochondrial DNA (mDNA) which is recognized internally by TLR9 and stimulate inflammatory cytokines. Recent CRISPR-CAS9 based screenings have also identified TLR9 to be one of the host factors which are important for SARS-CoV-2 replication. A recently published article hypothesized that TLR9 might play a critical role in COVID-19 pathogenesis. Presence of TLR9 on lung epithelial cells and CpG hotspots among SARS-CoV-2 genome further points towards a possible interplay among TLR9 and SARS-CoV-2. It was observed that the Envelop and ORF10 proteins of SARS-CoV-2 had an over-representation of CpG motifs suggesting that TLR9 might play a critical role in SARS-CoV-2 pathogenesis.

### Conclusions

After the onset of recent pandemic of COVID-19, several studies on SARS-CoV-2 and host protein–protein interactions have helped gain important insights into the viral pathogenesis. The insights obtained from these studies will be useful in developing effective and specific anti-viral targets to prevent the spread of the virus and treat the infected patients. Each and every study acts like a small step towards understanding the biology of the viral pathogenesis. In this report, four studies aiming to identify host factors critical for SARS-CoV-2 infection and replication were compared. Though the studies were performed under diverse experimental conditions, comparative analysis of CRISPR/Cas data from these studies led us to the identification of the host factors that were common among them. The host factors thus identified are known to regulate diverse cellular processes. Apart from SARS-CoV-2, most of the host factors were shown to be involved with the regulation of other viruses as well. Further insights on the importance of these host factors in SARS-CoV-2 replication and infection were obtained from the Biogrid database. The association of these host factors with SARS-CoV-2 proteins was extracted from the database and it was observed that apart from the CRISPR/Cas screens, most of these host factors were found to be associated with viral proteins also. Some of the host factors including GDI2, SLC35B2, LIMA1, VPS26A and ALG6 were found to be associated with multiple SARS-CoV-2 proteins thereby suggesting their importance in viral life cycle.

Gene ontology analysis of these host factors revealed that around 73% of identified host factors were associated with cellular membranes (GO:16020). Literature analysis also revealed that all the host factors except CSNK2B, ARPP-19 and BCOR were associated with cellular membranes. Among the membrane associated host factors, GDI2, ALG6, SLC35B2, COG3, VPS26A and LIMA1 were found to be associated with multiple SARS-CoV-2 proteins. Viruses have been known to rearrange host cell membranes for their optimal replication. Coronavirus non-structural proteins have been shown to induce membrane-rearrangement and double membrane vesicles in host cells. Therefore, it can be hypothesized that
viral proteins might co-opt these host factors for extensive membrane re-arrangement of host cells in order to create a conducive environment for viral replication. Moreover, RNA viruses have been known to induce replication organelles which shield viral RNA from cytoplasmic interferon sensors. Therefore, SARS-CoV-2 might utilize this strategy to induce extensive membrane vesicles by modulating these host factors to dampen the host interferon responses.

This review points towards the role of critical host factors in the biology of SARS-CoV-2. Many of these host factors interact with viral proteins, facilitating viral replication. For instance, ACE2 interacts with viral S protein, GDI2 interacts with viral NSP4, NSP6, M, ORF3B and ORF7B proteins. SLC35B2 interacts with viral S, M, NSP 4, NSP5, NSP6, ORF3A, ORF7A, ORF7B, NSP13 and NSP14 proteins. COG8 is known to interact with viral NSP14 protein. VPS26A interacts with viral S, M, E, NSP4, NSP5, NSP6, NSP13, ORF3A, ORF3B, ORF6, ORF7A, ORF7B and ORF8 proteins. CSNK2B has been found to interact with viral N protein. LRRN2 interacts with viral ORF3A and ORF7B proteins. DDX51 interacts with viral NSP6 and ORF14 proteins. COG3 interacts with viral ORF3B, ORF6, ORF7A and ORF7B proteins. ALG6 interacts with viral M, E, NSP4, ORF7A, ORF7B and ORF8 proteins. BCOR interacts with viral NSP7 and NSP16 proteins. ARPP-19, TLR9 and C1QTNF7 proteins have no known interactions with viral proteins. Some of them were further found to modulate other viruses as shown in figure.

Figure 1. The fifteen host proteins (ACE2, GDI2, TLR9, VPS26A, ARPP-19, SLC35B2, COG3, COG8, ALG6, BCOR, C1QTNF7, DDX51, LRRN2, CSNK2B, LIMA1) were found to be common in at least three recently published CRISPR screening of SARS CoV-2. ACE2 protein is known to interact with viral S protein. GDI2 interacts with viral NSP4, NSP6, M, ORF3B and ORF7B proteins. SLC35B2 interacts with viral S, M, NSP 4, NSP5, NSP6, ORF3A, ORF7A, NSP13 and NSP14 proteins. LIMA1 interacts with viral NSP2, NSP7, NSP10 and NSP14 proteins. COG8 is known to interact with viral NSP14 protein. VPS26A interacts with viral S, M, E, NSP4, NSP5, NSP6, NSP13, ORF3A, ORF3B, ORF6, ORF7A, ORF7B and ORF8 proteins. CSNK2B has been found to interact with viral N protein. LRRN2 interacts with viral ORF3A and ORF7B proteins. DDX51 interacts with viral NSP6 and ORF14 proteins. COG3 interacts with viral ORF3B, ORF6, ORF7A and ORF7B proteins. ALG6 interacts with viral M, E, NSP4, ORF7A, ORF7B and ORF8 proteins. BCOR interacts with viral NSP7 and NSP16 proteins. ARPP-19, TLR9 and C1QTNF7 proteins have no known interactions with viral proteins. Some of them were further found to modulate other viruses as shown in figure.
these host factors have been shown to modulate the pathogenesis of viruses of different families. Therefore, functional characterization of these host factors will help us gain insights not only for SARS-CoV-2 but many other viruses as well. Association of numerous viral proteins with these host factors further suggests how virus might use diverse strategies to modulate them. Though it is premature to draw conclusions, it is tempting to speculate on some possible avenues for further study. The findings of this latest research could turn out to be significant in the field of virology and presents unique opportunity to find new druggable pathways that could be utilized to combat the infection of not only the SARS-CoV-2 but also the any other virus.

**Funding**

Funding support was obtained from University Grants Commission, Government of India to VS (UGC-FRP) and Department of Science and Technology, Government of India (DST-INSPIRE Faculty) to SL, RM and AL.

**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.

**CRediT authorship contribution statement**

Sneh Lata: Data curation, Visualization. Ritu Mishra: Data curation. Ravi P. Arya: Data curation. Pooja Arora: Data curation. Anismrita Lahon: Data curation. Akhil C. Banerjea: Supervision, Data curation. Vikas Sood: Conceptualization, Supervision. Vikas Sood: Supervision, Data curation. Ravi P. Arya: Data curation. Anismrita Lahon: Data curation. Akhil C. Banerjea: Supervision, Data curation. Vikas Sood: Conceptualization, Supervision.

**Acknowledgements**

We acknowledge the funding from NII, DST and UGC. Authors are thankful to Neha Periwal for helping with the figure.

Received 17 August 2021; Accepted 7 December 2021; Available online 13 December 2021

**Keywords:**

COVID-19; SARS-CoV-2; CRISPR; host factors; viral diseases

**Abbreviations used:**

COVID-19, coronavirus disease 19; RRA, robust-rank aggregation; ACE2, angiotensin-converting enzyme 2; TMPRSS2, transmembrane protease serine 2; RSV, Respiratory Syncytial Virus; CSN2B, casein kinase 2 subunit beta; VACC, vaccinia virus; HPV, Human Papilloma Virus; HIV-1, Human Immunodeficiency Virus 1; HSV-1, Herpes Simplex Virus-1; GD12, GDP dissociation inhibitor beta; IAV, Influenza A virus; TMV, Tobacco Mosaic Virus; VSV, Vesicular Somatitis Virus; ChIKV, Chikungunya Virus; SLC35B2, solute carrier family 35 member B2; DENV, Dengue Virus; SBV, Schmallenberg virus; DDX, DEAD-box RNA helicase; VPS, vacuolar protein sorting; HCV, Hepatitis C virus; TBSV, Tomato bushy stunt virus; CIRV, Carnation Italian ringspot virus; ARPP-19, cyclic adenosine monophosphate-regulated phosphoprotein 19; PP2A, protein phosphatase 2A; HCC, hepatocellular carcinoma; C1QTNF7, C1q and tumor necrosis factor-related protein 7; CTRP, C1q complement/TNF-related protein; SNPs, single nucleotide polymorphisms; ALG, Alpha-1,3-glucosyltransferase; CDG5, carbohydrate-deficient glycoprotein syndrome; CDG1C, congenital disorder of N-linked glycosylation type 1C; LIMA-1, LIM domain and actin binding-1; EPLIN, epithelial protein lost in neoplasm; SREBP3, sterol regulatory element binding protein 3; COG, conserved oligomeric Golgi; BCOR, BCL6 interacting co-repressor; HDACS, histone deacetylases; EBV, Epstein–Barr virus; LRRN2, leucine-rich repeat neuronal protein 2; TLR, toll-like receptors

**References**

1. Wei, J., Alfajaro, M.M., DeWeirdt, P.C., Hanna, R.E., Lu-Culligan, W.J., Cai, W.L., Strine, M.S., et al., (2021). Genome-wide CRISPR Screens Reveal Host Factors Critical for SARS-CoV-2 Infection. Cell 184, 76–91.
2. Daniloski, Z., Jordan, T.X., Wessels, H.H., Hoagland, D.A., Kasela, S., Legut, M., Maniatis, S., et al., (2021). Identification of Required Host Factors for SARS-CoV-2 Infection in Human Cells. Cell 184, 92–105.
3. Wang, R., Simoneau, C.R., Kulpakash, J., Bouhaddou, M., Travisano, K.A., Hayashi, J.M., Carlson-Stevermer, J., et al., (2021). Genetic Screens Identify Host Factors for SARS-CoV-2 and Common Cold Coronaviruses. Cell 184, 106–119.
4. Schneider, W.M., Luna, J.M., Hoffmann, H.H., Sánchez-Rivera, F.J., Leal, A.A., Ashbrook, A.W., Le Pen, J., et al., (2021). Genome-Scale Identification of SARS-CoV-2 and Pan-coronavirus Host Factor Networks. Cell 184, 120–132.
5. Crowley, S.D., Gurley, S.B., Oliverio, M.J., Pazzmo, A.K., Giffiths, R., Flannery, P.J., Spurney, R.F., et al., (2005). Distinct roles for the kidney and systemic tissues in blood pressure regulation by the renin-angiotensin system. J. Clin. Invest. 115, 1092–1099.
6. Hamming, I., Timens, W., Bulthuis, M.L., Lely, A.T., Navis, G., van Goor, H., (2004). Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J. Pathol. 203, 631–637.
7. Chamsi-Pasha, M.A., Shao, Z., Tang, W.H., (2014). Angiotensin-converting enzyme 2 as a therapeutic target for heart (cardiac) failure. Curr. Heart. Fail. Rep. 11, 58–63.

8. Hofmann, H., Pyrc, K., van der Hoek, L., Geier, M., Berkhourt, B., Pohlmann, S., (2005). Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. Proc. Natl. Acad. Sci. USA 102, 7988–7993.

9. Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., Huan, Y., et al., (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nature Med. 11, 875–879.

10. Fehr, A.R., Perlman, S., (2015). Coronavirus infections: an overview of their replication and pathogenesis. Methods. Mol. Biol. 1282, 1–23.

11. Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., Zhong, W., et al., (2020). Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci. China. Life. Sci. 63, 457–460.

12. Senapat, S., Banerjee, P., Bhagavatula, S., Kushwaha, P.P., Kumar, S., (2021). Contributions of human ACE2 and TMPRSS2 in determining host-pathogen interaction of COVID-19. J. Gen. Virol. 102, 12.

13. Wang, H., Yang, P., Liu, K., Guo, F., Zhang, Y., Zhang, G., Jiang, C., (2008). SARS coronavirus entry into host cells through a novel clathrin- and caveolin-independent endocytic pathway. Cell Res. 18, 290–301.

14. Millet, J.K., Whittaker, G.R., (2018). Physiological and molecular triggers for SARS-CoV membrane fusion and entry into host cells. Virology 517, 3–8.

15. Matsuyma, S., Nagata, N., Shirato, K., Kawase, M., Takeda, M., Taguchi, F., (2010). Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMRPSS2. J. Virol. 84, 12659–12664.

16. Glowacka, I., Bertram, S., Müller, M.A., Allen, P., Soilleux, E., Pfefferle, S., Steffen, I., et al., (2011). Evidence that TMRPSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J. Virol. 85, 4122–4134.

17. Shulla, A., Heald-Sargent, T., Subramanya, G., Zhao, J., Perlman, S., Gallager, T., (2011). A transmembrane serine protease is linked to the severe acute respiratory syndrome coronavirus receptor and activates virus entry. J. Virol. 85, 873–882.

18. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T.S., et al., (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMRPSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 181, 271–280.

19. Dijkman, R., Jebbink, M.F., de Jaes, M., Miedema, A., Pyrc, K., Buelow, E., van der Bijl, A., et al., (2012). Replication-dependent downregulation of cellular angiotensin-converting enzyme 2 protein expression by human coronavirus NL63. J. Gen. Virol. 93, 1924–1929.

20. Imai, Y., Kuba, K., Penninger, J.M., (2008). The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. Exp. Physiol. 93, 543–548.

21. Jia, H., (2016). Pulmonary Angiotensin-Converting Enzyme 2 (ACE2) and Inflammatory Lung Disease. Shock 46, 239–248.

22. Zou, Z., Yan, Y., Shu, Y., Gao, R., Sun, Y., Li, X., Ju, X., et al., (2014). Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. Nature Commun. 5

23. Yang, P., Gu, H., Zhao, Z., Wang, W., Cao, B., Lai, C., Yang, X., et al., (2014). Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. Sci. Rep. 4

24. Liu, X., Yang, N., Tang, J., Liu, S., Luo, D., Duan, Q., Wang, X., (2014). Downregulation of angiotensin-converting enzyme 2 by the neuraminidase protein of influenza A (H1N1) virus. Virus. Res. 185, 64–71.

25. Gu, H., Xie, Z., Li, T., Zhang, S., Lai, C., Zhu, P., Wang, K., et al., (2016). Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. Sci Rep. 6, 19840

26. Litchfield, D.W., (2003). Protein kinase CK2: Structure, regulation and role in cellular decisions of life and death. Biochem. J. 369, 1–15.

27. Poirier, K., Hubert, L., Viot, G., Rio, M., Billuart, P., Besmond, C., Bienvenu, T., (2017). CSNK2B splice site mutations in patients cause intellectual disability with or without myoclonic epilepsy. Hum Mutat. 38, 932–941.

28. Li, J., Gao, K., Cai, S., Liu, Y., Wang, Y., Huang, S., Zha, J., (2019). Germline de novo variants in CSNK2B in Chinese patients with epilepsy. Sci. Rep. 9, 17909.

29. Buchou, T., Vernet, M., Blond, O., Jensen, H.H., Pointu, H., Olsen, B.B., Cochet, C., et al., (2003). Disruption of the regulatory beta subunit of protein kinase CK2 in mice leads to a cell-autonomous defect and early embryonic lethality. Mol. Cell. Biol. 23, 908–915.

30. Glover, K.K.M., Gao, A., Zahed-Amiri, A., Coombs, K.M., (2019). Vero Cell Proteomic Changes Induced by Zika Virus Infection. Proteomics 19, e1800309

31. Chasapis, C.T., Georgiopoulou, A.K., Perlepes, S.P., Bjerklund, G., Peana, M., (2021). A SARS-CoV-2 - human metalloproteome interaction map. J Inorg Biochem. 219, 11423.

32. Marjuki, H., Scholtissek, C., Yen, H.L., Webster, R.G., (2008). CK2beta gene silencing increases cell susceptibility to influenza A virus infection resulting in accelerated virus entry and higher viral protein content. J. Mol. Signal. 3, 13.

33. Alvarez, D.E., Agaisse, H., (2012). Casein kinase 2 regulates vaccinia virus actin tail formation. Virology 423, 143–151.

34. Piirsoo, A., Piirsoo, M., Kala, M., Sankovski, E., Lototskaja, E., Levin, V., Salvi, M., et al., (2019). Activity of CK2x protein kinase is required for efficient replication of some HPV types. PLoS Pathog. 15, e1007788.

35. Meggio, F., D’Agostino, D.M., Cinimale, V., Chieco-Bianchi, L., Pinna, L.A., (1996). Phosphorylation of HIV-1 Rev protein: implication of protein kinase CK2 and pro-directed kinases. Biochim. Biophys. Res. Commun. 226, 547–554.

36. Ohtsuki, K., Maekawa, T., Harada, S., Karino, A., Morikawa, Y., Ito, M., (1998). Biochemical characterization of HIV-1 Rev as a potent activator of casein kinase II in vitro. FEBS Letters 428, 235–240.

37. Marin, O., Sarno, S., Boschetti, M., Pagano, M.A., Meggio, F., Cinimale, V., D’Agostino, D.M., et al., (2000). Unique features of HIV-1 Rev protein phosphorylation by protein kinase CK2 (casein kinase-2). FEBS Letters 481, 63–67.
38. Meggio, F., Marin, O., Boschetti, M., Sarno, S., Pinna, L. A., (2001). HIV-1 Rev transactivator: a beta- subunit directed substrate and effector of protein kinase CK2. *Mol. Cell. Biochem.* 227, 145–151.

39. Naji, S., Ambrus, G., Cimermančić, P., Reyes, J.R., Johnson, J.R., Filbrandt, R., Huber, M.D., et al., (2012). Host cell interactome of HIV-1 Rev includes RNA helicases involved in multiple facets of virus production. *Mol. Cell Proteomics* 11 M111.015313.

40. Schubert, U., Schneider, T., Henklein, P., Hoffmann, K., Berthold, E., Hauser, H., Pauli, G., et al., (1992). Human-immunodeficiency-virus-type-1-encoded Vpu protein is phosphorylated by casein kinase II. *Eur. J. Biochem.* 204, 875–883.

41. Schubert, U., Strehel, K., (1994). Differential activities of the human immunodeficiency virus type 1- encoded Vpu protein are regulated by phosphorylation and occur in different cellular compartments. *J. Virol.* 68, 2260–2271.

42. Schubert, U., Henklein, P., Boldyreff, B., Wingender, E., Streb., K., Porstmann, T., (1994). The human immunodeficiency virus type 1 encoded Vpu protein is phosphorylated by casein kinase-2 (CK-2) at positions Ser52 and Ser56 within a predicted alpha-helix-turn-alpha-helix-motif. *J. Mol. Biol.* 236, 16–25.

43. Friborg, J., Ladha, A., Göttlinger, H., Haseltine, W.A., Cohen, E.A., (1995). Functional analysis of the phosphorylation sites on the human immunodeficiency virus type 1 Vpu protein. *J. Acquir. Immune. Defic. Syndr. Hum. Retrovirol.* 8, 10–22.

44. Paul, M., Jabbar, M.A., (1997). Phosphorylation of both phosphoacceptor sites in the HIV-1 Vpu cytoplasmic domain is essential for Vpu-mediated ER degradation of CD4. *Virology* 232, 207–216.

45. Swingler, S., Gallay, P., Camaur, D., Song, J., Abo, A., Trono, D., (1997). The Nef protein of human immunodeficiency virus type 1 enhances serine phosphorylation of the viral matrix. *J. Virol.* 71, 4372–4377.

46. Haneda, E., Furuya, T., Asai, S., Morikawa, Y., Ohtsuki, K., (2000). Biochemical characterization of casein kinase II as a protein kinase responsible for stimulation of HIV-1 protease in vitro. *Biochem. Biophys. Res. Commun.* 275, 434–439.

47. Harada, S., Maekawa, T., Haneda, E., Morikawa, Y., Nagata, N., Ohtsuki, K., (1998). Biochemical characterization of recombinant HIV-1 reverse transcriptase (rRT) as a glycoythin-binding protein and the CK-II-mediated stimulation of rRT activity potently inhibited by glycyrrhetinic acid derivative. *Biol. Pharm. Bull.* 12, 1282–1285.

48. Harada, S., Haneda, E., Maekawa, T., Morikawa, Y., Funayama, S., Nagata, N., Ohtsuki, K., et al., (1999). Casein kinase II (CK-II)-mediated stimulation of HIV-1 reverse transcriptase activity and characterization of selective inhibitors in vitro. *Biol. Pharm. Bull.* 10, 1122–1126.

49. Idriss, H., Kawa, S., Damuni, Z., Thompson, E.B., Wilson, S.H., (1999). HIV-1 reverse transcriptase is phosphorylated in vitro and in a cellular system. *Int. J. Biochem.* 31, 1443–1452.

50. Lazar, J.B., Boretto, J., Selmi, B., Capony, J.P., Canard, B., (2000). Phosphorylation of AZT-resistant human immunodeficiency virus type 1 reverse transcriptase by casein kinase II in vitro: effects on inhibitor sensitivity. *Biochem. Biophys. Res. Commun.* 275, 26–32.
66. Fang, R., Jiang, Q., Guan, Y., Gao, P., Zhang, R., Zhao, Z., Jiang, Z., (2021). Golgi apparatus-synthesized sulfated glycosaminoglycans mediate polymerization and activation of the cGAMP sensor STING. *Immunity*. 54, 962–975.

67. Park, R.J., Wang, T., Koundakjian, D., Hultquist, J.F., Lamotho-Molina, P., Monel, B., Schumam, K., et al., (2017). A genome-wide CRISPR screen identifies a restricted set of HIV host dependency factors. *Nature Genet.* 49, 193–203.

68. Robinson-McCarthy, L.R., McCarthy, K.R., Raaben, M., Piccinotti, S., Nieuwenhuis, J., Stubbs, S.H., Bakkers, M.J.G., et al., (2018). Reconstruction of the cell entry pathway of an extinct virus. *PloS Pathog.* 14 e1007123.

69. Srivastava, L., Lapik, Y.R., Wang, M., Pestov, D.G., Fang, R., Jiang, Q., Guan, Y., Gao, P., Zhang, R., Zhao, et al., (2021). The retromer is a multi-allelic origin of congenital disorder of glycosylation syndrome type-Ic. *Proc. Natl. Acad. Sci. USA* 96, 6987–6997.

70. Wang, X., Liu, H., Zhao, C., Li, W., Xu, H., Chen, Y., et al., (2016). Novel insights into human small cell lung cancer proliferation by regulating cell cycle progression via multiple pathways. *Sci. Rep.* 6, 26108.

71. Nicol, S.M., Bray, S.E., Derek, Black, H., Lornore, S.A., Wright, E.G., Lane, D.P., et al., (2013). The RNA helicase p68 (DDX5) is selectively required for the induction of p53-dependent p21 expression and cell-cycle arrest after DNA damage. *Oncogene* 32, 3461–3469.

72. Wang, Z., Luo, Z., Zhou, L., Li, X., Jiang, T., Fu, E., et al., (2015). DDX5 promotes proliferation and tumorigenesis of non-small-cell lung cancer cells by activating f-catenin signaling pathway. *Cancer Sci.* 106, 1303–1312.

73. Squeglia, F., Romano, M., Ruggiero, A., Maga, G., Berisio, R., (2020). Host DDX helicases as possible SARS-CoV-2 proviral factors: a structural overview of their hijacking through multiple viral proteins. *Front. Chem.* 8, 602162.

74. Dapat, C., Oshitani, H., (2016). Novel insights into human respiratory syncytial virus-host factor interactions through integrated proteomics and transcriptomics analysis. *Expert. Rev. Anti. Infect. Ther.* 14, 285–297.

75. Trousdale, C., Kim, K., (2015). Retromer: structure, function, and roles in mammalian disease. *Eur. J. Cell Biol.* 94, 513–521.

76. Starble, R., Pokrywka, N.J., (2018). The retromer subunit Vps26 mediates notch signaling during Drosophila oogenesis. *Mech. Dev.* 149, 1–8.

77. Yin, P., Hong, Z., Yang, X., Chung, R.T., Zhang, L., (2016). A role for retromer in hepatitis C virus replication. *Cell. Mol. Life. Sci.* 73, 869–881.

78. Groppelli, E., Len, A.C., Granger, L.A., Jolly, C., (2014). Retromer regulates HIV-1 envelope glycoprotein trafficking and incorporation into virosomes. *PloS Pathog.* 10, e1004518.

79. Feng, Z., Inaba, J.I., Nagy, P.D., (2021). The retromer is co-opted to deliver lipid enzymes for the biogenesis of lipid-enriched tumbiralvirus replication organelles. *Proc. Natl. Acad. Sci. USA* 118 e2016066118.

80. Horiuchi, A., Williams, K.R., Kurihara, T., Naim, A.C., Greengard, P., (1990). Purification and cDNA cloning of ARPP-16, a cAMP-regulated phosphoprotein enriched in basal ganglia, and of a related phosphoprotein, ARPP-19. *J. Biol. Chem.* 265, 9475–9484.

81. Inrwin, N., Chao, S., Gortichenko, L., Horiuchi, A., Greengard, P., Naim, A.C., Benowitz, L.I., (2002). Nerve growth factor controls GAP-43 mRNA stability via the phosphoprotein ARPP-19. *Proc. Natl. Acad. Sci. USA* 99, 12427–12431.

82. Kim, S. H., Nairn, A. C., Cairns, N. & Lubec, G. Decreased levels of ARPP-19 and PKA in brains of Down syndrome and Alzheimer’s disease. *J. Neural. Transm. Suppl.* 61, 263–272.

83. Gharbi-Ayachi, A., Labbé, J.C., Burgess, A., Vigneron, S., Strub, J.M., Brioudes, E., Van-Dorselaer, A., et al., (2010). The substrate of Greatwall kinase, Arpp19, controls mitosis by inhibiting protein phosphatase 2A. *Science* 330, 1673–1677.

84. Haccard, O., Jessus, C., (2011). Greatwall kinase, ARPP-19 and protein phosphatase 2A: shifting the mitosis paradigm. *Results. Probl. Cell. Differ.* 53, 219–234.

85. Okumura, E., Morita, A., Wakai, M., Mochida, S., Harai, M., Kishimoto, T., (2014). Cyclin B-Cdk1 inhibits protein phosphatase PP2A-B55 via a Greatwall kinase-independent mechanism. *J. Cell. Biol.* 204, 881–889.

86. Mochida, S., Maslen, S.L., Skehel, M., Hunt, T., (2010). Greatwall phosphorylates an inhibitor of protein phosphatase 2A that is essential for mitosis. *Science* 330, 1670–1673.

87. Wang, Z., Luo, Z., Hug, C., Taso, T.S., Lodish, H.F., (2004). A family of Acpr30/adiponectin structural and functional paralogs. *Proc. Natl. Acad. Sci. USA* 101, 10302–10307.

88. Seccia, T.M., Ferraro, S., Belloni, A.S., Skander, G., Lenzini, L., Pessina, A.C., Rossi, G.P., (2010). The novel identified adipokines CTRP (Complement-C1q Tnf-Related Protein)-5, CTRP-6, and CTRP-7 are expressed in the adrenal gland and in peridrenal fat tissue. *PP.18.176. J. Hypertension* 28 Article 302.

89. Petersen, P.S., Lei, X., Wolf, R.M., Rodriguez, S., Tan, S.Y., Little, H.C., Schweitzer, M.A., et al., (2017). CTRP7 deletion attenuates obesity-linked glucose intolerance, adipose tissue inflammation, and hepatic stress. *Am. J. Physiol. Endocrinol. Metab.* 312, E309–E325.

90. Dick, D.M., Aliev, F., Krueger, R.F., Edwards, A., Agrawal, A., Lynskey, M., Lin, P., et al., (2011). Genome-wide association study of conduct disorder symptomatology. *Mol. Psychiatry* 16, 800–808.

91. Zhang, Y., Liu, C., Liu, J., Guo, R., Yan, Z., Liu, W., Lau, W.B., et al., (2020). Implications of C1q/TNF-related protein superfamily in patients with coronary artery disease. *Sci. Rep.* 10, 878.

92. Al-Garawi, A., Husain, M., Ilieva, D., Humbles, A.A., Kolbeck, R., Stampfl, M.R., O’Byrne, P.M., et al., (2012). Shifting of immune responsiveness to house dust mite by influenza A infection: genomic insights. *J. Immunol.* 188, 832–843.

93. Jaeken, J., Lefeber, D., Matthijs, G., (2015). Clinical utility gene card for: ALG1 defective congenital disorder of glycosylation. *Eur. J. Hum. Genet.* 23, 1431.

94. Imbach, T., Burda, P., Kuhnert, P., Wevers, R.A., Aebl, M., Berger, E.G., Henret, T., (1999). A mutation in the human ortholog of the Saccharomyces cerevisiae ALG6 gene causes carbohydrate-deficient glycoprotein syndrome type-Ic. *Proc. Natl. Acad. Sci. USA* 96, 6982–6987.

95. Imbach, T., Grönewald, S., Schenk, B., Burda, P., Schollen, E., Wevers, R.A., Jaeken, J., et al., (2000). Multi-allelic origin of congenital disorder of glycosylation (CDG)-Ic. *Hum. Genet.* 106, 538–545.
96. Westphal, V., Schottstädt, C., Marquardt, T., Freeze, H. H., (2000). Analysis of multiple mutations in the hALG6 gene in a patient with congenital disorder of glycosylation Ic. *Mol. Genet. Metab.* **70**, 219–223.

97. Zhou, B., Zhao, Y.C., Liu, H., Luo, S., Amos, C.I., Lee, J., Li, X., et al., (2020). Novel Genetic Variants of ALG6 and GALNT4 of the Glycosylation Pathway Predict Cutaneous Melanoma-Specific Survival. *Cancers (Basel)* **12**, 288.

98. Maul, R., Chang, D., (1999). EPLIN, Epithelial protein lost in neoplasm. *Oncogene* **18**, 7838–7841.

99. Schmeichel, K.L., Beckerle, M.C., (1997). Molecular dissection of a LIM domain. *Mol. Biol. Cell.* **8**, 219–230.

100. Jiang, W.G., Martin, T.A., Lewis-Russell, J.M., Douglas-Jones, A., Ye, L., Mansel, R.E., (2008). Eplin-alpha expression in human breast cancer, the impact on cellular migration and clinical outcome. *Mol. Cancer* **7**, 71.

101. Zhang, S., Wang, X., Osunkoya, A.O., Iqbal, S., Wang, Y., Chen, Z., Müller, S., et al., (2011). EPLIN downregulation promotes epithelial-mesenchymal transition in prostate cancer cells and correlates with clinical lymph node metastasis. *Oncogene* **30**, 4941–4952.

102. Liu, Y., Sanders, A.J., Zhang, L., Jiang, W.G., (2012). EPLIN-α expression in human osteosarcoma cancer and its impact on cellular aggressiveness and clinical outcome. *Anticancer Res.* **32**, 1283–1289.

103. Song, Y., Maul, R.S., Gerbin, C.S., Chang, D.D., (2002). Inhibition of anchorage-independent growth of transformed NIH3T3 cells by epithelial protein lost in neoplasm (EPLIN) requires localization of EPLIN to actin cytoskeleton. *Mol. Biol. Cell.* **13**, 1408–1416.

104. Maul, R.S., Song, Y., Amann, K.J., Gerbin, S.C., Pollard, T.D., Chang, D.D., (2003). EPLIN regulates actin dynamics by cross-linking and stabilizing filaments. *J. Cell. Biol.* **160**, 399–407.

105. Abe, K., Takeichi, M., (2008). EPLIN mediates linkage of the cadherin catenin complex to F-actin and stabilizes the circumferential actin belt. *Proc. Natl. Acad. Sci. USA* **105**, 13–19.

106. Ohashi, T., Idogawa, M., Sasaki, Y., Tokino, T., (2017). p53 mediates the suppression of cancer cell invasion by inducing LIMA1/EPLIN. *Cancer Letters* **390**, 58–66.

107. Collins, R.J., Jiang, W.G., Hardest, R., Mason, M.D., Sanders, A.J., (2015). EPLIN: a fundamental actin regulator in cancer metastasis? *Cancer. Metastasis. Rev.* **34**, 753–764.

108. Wu, D., (2017). Epithelial protein lost in neoplasm (EPLIN): Beyond a tumor suppressor. *Genes. Dis.* **4**, 100–107.

109. Zhang, Y.Y., Fu, Z.Y., Wei, J., Qi, W., Baituola, G., Luo, J., Meng, Y.J., et al., (2018). A LIMA1 variant promotes low plasma LDL cholesterol and decreases intestinal cholesterol absorption. *Science* **360**, 1087–1092.

110. Wruck, W., Adjaye, J., (2020). SARS-CoV-2 receptor ACE2 is co-expressed with genes related to transmembrane serine proteases, viral entry, immunity and cellular stress. *Sci. Rep.* **10**, 21415.

111. Rymen, D., Winter, J., Van Hasselt, P.M., Jaeken, J., Kasapkarpa, C., Gokçay, G., Hajjes, H., et al., (2015). Key features and clinical variability of COG6-CDG. *Mol. Genet. Metab.* **116**, 163–170.

112. Liu, S., Dominska-Ngowe, M., Dykhooorn, D.M., (2014). Target silencing of components of the conserved oligomeric Golgi complex impairs HIV-1 replication. *Virus. Res.* **192**, 92–102.

113. Ungar, D., Oka, T., Vasile, E., Krieger, M., Hughson, F.M., (2005). Subunit architecture of the conserved oligomeric Golgi complex. *J. Biol. Chem.* **280**, 32729–32735.

114. Ma, Y., Wu, L., Shaw, N., Gao, Y., Wang, J., Sun, Y., Lou, Z., et al., (2015). Structural basis and functional analysis of the SARS coronavirus nsp14-nsp10 complex. *Proc. Natl. Acad. Sci. USA* **112**, 9436–9441.

115. Realegeno, S., Priyamvada, L., Kumar, A., Blackburn, J. B., Hartлоге, C., Puschnik, A.S., Sambhara, S., (2020). Conserved Oligomeric Golgi (COG) Complex Proteins Facilitate Orthopoxvirus Entry, Fusion and Spread. *Viruses* **12**, 707.

116. Pettitjean, O., Girardi, E., Ngondo, R.P., Lupashin, V., Pfeffer, S., (2020). Genome-Wide CRISP-PR-Cas9 Screen Reveals the Importance of the Heparan Sulfate Pathway and the Conserved Oligomeric Golgi Complex for Synthetic Double-Stranded RNA Uptake and Sindbis Virus infection. mSphere, e00914-20.

117. Riblett, A.M., Blomen, V.A., Jae, L.T., Altamura, L.A., Dom, R.W., Brummelkamp, T.R., Wojcieszowskyj, J.A., (2015). A Haploid Genetic Screen Identifies Heparan Sulfate Proteoglycans Supporting Rift Valley Fever Virus Infection. *J. Virol.* **90**, 1414–1423.

118. Kelly, M.J., So, J., Rogers, A.J., Gregory, G., Li, J., Zethoven, M., Gearhart, M.D., et al., (2019). Bcor loss perturbs myeloid differentiation and promotes leukemogenesis. *Nat. Commun.* **10**, 1347.

119. Huynh, K.N., Fischle, W., Verdin, E., Bardwell, V.J., (2000). BCoR, a novel corepressor involved in BCL-6 repression. *Genes Dev.* **14**, 1810–1823.

120. Choi, J., Diao, H., Faliti, C.E., Truong, J., Rossi, M., Bélangér, S., Yu, B., Goldrath, A.W., et al., (2020). Bcl-6 is the nexus transcription factor of T follicular helper cells via repressor-of-repressor circuits. *Nature Immunol.* **21**, 777–789.

121. O’Brien, S.A., Zhu, M., Zhang, W., (2021). Spontaneous Differentiation of T Follicular Helper Cells in LATY136F Mutant Mice. *Front. Immunol.* **12**, 656817.

122. Gonzalez-Figueroa, P., Roco, J.A., Papa, I., Núñez-Villacís, L., Stanley, M., Linterman, M.A., Dent, A., et al., (2021). Follicular regulatory T cells produce neurotin to regulate B cells. *Cell* **184**, 1775-1789.e19.

123. Choi, W.I., Jeon, B.N., Yoon, J.H., Koh, D.I., Kim, M.H., Yu, M.Y., Lee, K.M., et al., (2013). The proto-oncoprotein FBI-1 interacts with MBD3 to recruit the Mi-2/NuRD-HDAC complex and BCoR and to silence p21WAF/CDKN1A by DNA methylation. *Proc. Natl. Acad. Sci. USA* **110**, 2342.

124. Gearhart, M.D., Corcoran, C.M., Wamstad, J.A., Bardwell, V.J., (2006). Polycomb group and SCF ubiquitin ligases are found in a novel BCOR complex and to silence p21WAF/CDKN1A by DNA methylation. *Nucleic Acids Res.* **41**, 6403–6420.

125. Kirchdoerfer, R.N., Ward, A.B., (2019). Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. *Nat. Commun.* **10**, 2342.

126. Almeida, A., Zhu, X.X., Vogt, N., Tyagi, R., Muleris, M., Dutrillaux, A.M., Dutrillaux, B., et al., (1998). GAC1, a new member of the leucine-rich repeat superfamily on chromosome band 1q22.1, is amplified and overexpressed in malignant gliomas. *Oncogene* **16**, 2997–3002.
127. Hamano, S., Ohira, M., Isogai, E., Nakada, K., Nakagawara, A., (2004). Identification of novel human neuronal leucine-rich repeat (hNLRR) family genes and inverse association of expression of Nbla10449/hNLRR-1 and Nbla10677/hNLRR-3 with the prognosis of primary neuroblastomas. Int. J. Oncol. 24, 1457–1466.

128. Van-Boheemen, S., de-Graaf, M., Lauber, C., Bestebroer, T.M., Raj, V.S., Zaki, A.M., Osterhaus, A.D., et al. (2012). Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. mBio 3, e00473-12.

129. Choi, J., Kim, M.G., Oh, Y.K., Kim, Y.B., (2017). Progress of Middle East respiratory syndrome coronavirus vaccines: a patent review. Expert Opin. Ther. Pat. 27, 721–731.

130. Kaisho, T., Akira, S., (2006). Toll-like receptor function and signaling. J. Allergy Clin. Immunol. 117, 979–987. ; quiz 988.

131. Medzhitov, R., (2001). Toll-like receptors and innate immunity. Nature Rev. Immunol. 1, 135–145.

132. Yang, Y., Wang, C., Cheng, P., Zhang, X., Li, X., Hu, Y., Xu, F., et al., (2018). CD180 Ligation Inhibits TLR7- and TLR9-Mediated Activation of Macrophages and Dendritic Cells Through the Lyn-SHP-1/2 Axis in Murine Lupus. Front. Immunol. 9, 2643.

133. Karapetyan, L., Luke, J.J., Davar, D., (2020). Toll-Like Receptor 9 Agonists in Cancer. Onco Targets Ther. 13, 10039–10060.

134. Kumar, V., (2021). The Trinity of cGAS, TLR9, and ALRs Guardians of the Cellular Galaxy Against Host-Derived Self-DNA. Front. Immunol. 11, 624597

135. Arankalle, V.A., Lole, K.S., Arya, R.P., Tripathy, A.S., Ramdasi, A.Y., Chadha, M.S., Sangle, S.A., et al., (2010). Role of host immune response and viral load in the differential outcome of pandemic H1N1 (2009) influenza virus infection in Indian patients. PLoS One. 5, e13099.

136. Lai, J.H., Wang, M.Y., Huang, C.Y., Wu, C.H., Hung, L.F., Yang, C.Y., Ke, P.Y., et al., (2018). Infection with the dengue RNA virus activates TLR9 signaling in human dendritic cells. EMBO Rep. 19, e46182.

137. Bezemer, G.F.G., Garssen, J., (2021). TLR9 and COVID-19: A Multidisciplinary Theory of a Multifaceted Therapeutic Target. Front. Pharmacol. 11, 601685

138. Digard, P., Lee, H.M., Sharp, C., Grey, F., Gaunt, E., (2020). Intra-genome variability in the dinucleotide composition of SARS-CoV-2. Virus Evol. 6 veaa057.

139. Oughtred, R., Stark, C., Breitkreutz, B.J., Rust, J., Boucher, L., Chang, C., Kolas, N., et al., (2019). The BioGRID interaction database: 2019 update. Nucleic Acids Res. 47, D529–D541.

140. Oudshoorn, D., Rijs, K., Limpens, R.W.A.L., Groen, K., Koster, A.J., Snijder, E.J., Kikkert, M., et al. (2017). Expression and Cleavage of Middle East Respiratory Syndrome Coronavirus nsp3-4 Polypeptide Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronaviral RNA Replication. mBio 8, e01658-17.

141. Scutigliani, E.M., Kikkert, M., (2017). Interaction of the innate immune system with positive-strand RNA virus replication organelles. Cytokine Growth Factor Rev. 37, 17–27.