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Where all the Roads Meet? A Crossover Perspective on Host Factors Regulating SARS-CoV-2 infection

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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/Cas 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.

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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.² 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, JMJD6, 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,¹ endosomal protein sorting Retromer complex: VPS26A, VPS29, VPS35, and SNX27 and endosomal trafficking Commander complex: COMMD2, COMMD3, COMMD3-BMI1, and COMMD4²; vacuolar-ATPase proton pump: ATP6AP1, ATP6AP2, ATP6V0B, ATP6V0C, ATP6V0D1, ATP6V1A (involved in cholesterol metabolism),³ host factors involved in pathways related to heparan sulphate biosynthesis and transport (such as EXT1, EXT2, EXTL3, B3GALT6, B3GAT3, B4GALT7, SLC35B2, XYLT2, 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)⁴; and 3 members of the PI3K pathway: PIK3C3/VPS34, WDR81, and ACP5 (involved in phosphatidylinositol biosynthetic processes).^{2,3} The genes involved in Nucleosome Remodeling Factor (NURF) complex were identified as anti-viral factors for corona viruses.¹ Endoplasmic reticulum membrane protein complex (EMC), the DEAH-box helicases DHX36 and DHX38, factors from Golgi family (GOLGA6L1 and GOLGA80), 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 phosphatidylethanolamine biosynthesis (PCYT2 and EPT) were also found to be interacting with SARS-CoV-2 as identified in the screen.⁴ 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 (GDP 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.⁵ 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.⁶ It lowers the blood pressure by catalysing the hydrolysis of angiotensin II into angiotensin 1-7.⁷

Being a transmembrane protein, ACE2 has been identified to serve as the entry point into the host cells for coronaviruses HCoV-NL63,⁸ SARS-CoV^{9,10} and SARS-CoV-2 (the virus that causes COVID-19).^{11,12} 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).¹⁵⁻¹⁸ The interaction of ACE2 and spike protein of coronaviruses reduces the levels of ACE2¹⁹ due to its

internalization and degradation in the endosomes which may result in the lung damage.^{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.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.^{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.²⁵

CSNK2B

Casein kinase 2 subunit beta (CSNK2B) is the beta subunit of casein kinase 2 (CSNK2) protein. CSNK2 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 α and two β subunits. Different species may have two related forms of alpha subunits i.e. α and α' or two related forms of beta subunits i.e. β and β' . 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.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.^{27,28} CSNK2B knockout mice have been found to be embryonically lethal.²⁹

CSNK2B has been recently found to interact with N protein of SARS-CoV-2 and is critical for viral infection.^{1–4} Recent proteomics based studies also identified CSNK2B as one of the interacting partners during Zika virus and SARS-CoV-2 infections.^{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.³² Inhibition of CSNK2 impaired Vaccinia virus (VACV) dissemination and actin tail formation.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.³⁴ CSNK2 has been reported to phosphorylate many HIV-1 (Human Immunodeficiency Virus 1) proteins such as Rev,^{35–39} Vpu,^{40–44} Matrix,⁴⁵ protease⁴⁶ and reverse transcriptase^{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.⁵¹ The association of CSNK2B with various diverse viruses further point towards its critical role in SARS-CoV-2 viral biology.

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.^{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.^{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.⁵⁶ GDI2 was also found to be associated with Vesicular Stomatitis Virus (VSV) virions.⁵⁷ GDI2 was also reported to be associated with Chikungunya Virus (CHIKV) infection.⁵⁸ It was also found to be differentially regulated in avian influenza infected chicken embryo fibroblasts.⁵⁹ The expression of GDI2 was observed to be up-regulated during Zika virus (ZIKV) infection.⁶⁰ Interestingly, a recent deep learning based study identified GDI2 among top 10 host factors that could be modulated to inhibit coronaviridae family viruses.⁶¹

SLC35B2

SLC35B2 is a solute carrier family 35 member B2 gene, encoding 3'-phosphoadenosine 5'-phosphosulfate (PAPS) transporter 1 (PAPST1) protein.⁶² This protein is involved in Heparan Sulphate proteoglycan synthesis and thus play a critical role in viral attachment to host cells and viral

entry.⁶³ 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 ZIKA virus, DENV (Dengue Virus) and many other viruses. In a knockout study of SLC35B2, it was found that entry process of ZIKA virus is not reduced but DENV virus attachment was impacted.⁶³ 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 such as La Crosse virus and Rift Valley fever virus were also found to depend on heparan sulphate for host cell infection.⁶⁵ Another study by Fang *et al.* showed that knockout of SLC35B2 inhibits GAG sulphation and it can restrict the immune responses against Vaccinia virus infection in mice.⁶⁶ SLC35B2 was also reported to be playing a part in tyrosine sulfation which is also crucial for HIV-1 infection.⁶⁷ The gene was also shown to be involved in the cell entry pathways of extinct endogenous retroviruses.⁶⁸

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.^{69,70} 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.⁷⁵

Being a member protein of a cellular house-keeping 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.^{1-4,52} 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

during HCV life cycle and therefore can be viewed as a potential therapeutic target also against HCV.⁷⁷ In HIV packaging and budding too, VPS35 and VPS26 have shown to interact the cytoplasmic tail of HIV-1 Env protein and therefore required for HIV-1 morphogenesis. Mutagenesis and co-immunoprecipitation studies establish that these retromer proteins and their function during trafficking are crucial in the late-stages of viral replication and assembly of HIV-1.⁷⁸ Even in plants, these retromer proteins seem to play important role in the pathogenesis of tomato bushy stunt virus (TBSV) and the closely related carnation Italian ringspot virus (CIRV). These viruses hijack the retromer complex to facilitate their own viral particle formation and release.⁷⁹ The authors further reported that depletion of these retromer proteins strongly inhibit the replication of peroxisome associate TBSV and mitochondria associated CIRV in yeast and plants too thereby establishing the critical role of these retromer complexes in viral life cycle.⁷⁹

ARPP-19

Cyclic adenosine monophosphate-regulated phosphoprotein-19 (ARPP-19) was first identified in bovine brain⁸⁰ 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.⁸¹ Decreased levels of ARPP-19 have been associated with pathogenesis of Down syndrome and Alzheimer's disease.⁸² ARPP-19 has been shown to play a vital role in mitosis regulation in the cell. On getting phosphorylated by protein kinase Greatwall (Gwl) at serine^{83,84} or by cyclin B-Cdk1 at different site in Gwl-independent manner,⁸⁵ 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.⁸⁶ 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.¹⁻⁴ 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 paralogs⁸⁷ 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.⁸⁸ 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.⁸⁹ 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.⁹⁰ Recently, CTRP7 has been suggested as one of the markers for coronary artery disease.⁹¹

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.⁹² It was recently reported to play an important role in SARS-CoV-2 pathogenesis,¹⁻⁴ 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 glucosyltransferase. The enzyme enables the transfer of glucose to the lipid-linked growing oligosaccharide that is important for N-linked glycosylation of protein and fats.⁹³ The mutation of human ALG6 leads to Carbohydrate-Deficient Glycoprotein Syndrome (CDGS) type-1c⁹⁴ that 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.^{95,96} 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.⁹⁷

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-2.¹⁻⁴ 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.⁹⁸ It has a 54-residue centrally-located *lin-11*, *isl-1*, and *mec-3* (LIM) domain that allows it to interact with several proteins.⁹⁹ Majority of human epithelial cancer cell lines and cancers including breast, prostate and oesophageal show nil or very low expression of EPLIN/LIMA-1.^{98,100–102} 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.¹⁰³ It has been shown to play a crucial role in actin dynamics¹⁰⁴ via linking cadherin-catenin complex to F-actin¹⁰⁵ and stabilizing actin filaments. Ohashi *et al.* found that p53 mediates inhibition of cancerous cell invasion via LIMA-1 and considered LIMA-1 as one of the novel prognostic predictors for tumour¹⁰⁶ which has a potential in tumour suppression.^{107,108} In humans, one of the LIMA-1 variant has been shown to decrease absorption of intestinal cholesterol, thus lowering low-density lipoprotein cholesterol.¹⁰⁹ 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.^{1–4} It has also been shown to be associated with SARS-CoV-2 receptor ACE2¹¹⁰ 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-octamer 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.^{111,112} 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 8.¹¹³ Mutations in these COG proteins have been detected in patients with congenital disorders of glycosylation (CDG) of variable severity.¹¹¹

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.^{1–4} 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 inter-

act with NSP14 protein of SARS-CoV-2⁵² 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.¹¹⁴ 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.¹¹⁵ 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 MAJI cells.¹¹² 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.¹¹⁶ Another study utilizing haploid genetic screen further confirmed the involvement of all COG molecules (except that of COG6) in Rift Valley Fever Virus infection.¹¹⁷ 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.¹¹⁸ BCOR was identified as the co-repressor involved in BCL6 repression.¹¹⁹ BCOR has two functional domains: the BCL6-binding domain that interacts specifically with the transcriptional repressor BCL6 and PUF 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.^{120–122} BCOR has been reported for the interaction with histone deacetylases (HDACS)^{123,119} and also engages in macromolecular complexes for epigenetic modifications to direct gene silencing.¹²⁴

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 BCOR genes.¹²⁵ Recent CRISPR-CAS9 based screenings showed that BCOR is required for SARS-CoV-2 pathogenesis.^{1–4} Recently, BCOR has also been

found to interact with NSP7 and NSP16 proteins of SARS-CoV-2⁵² which are required for the virus replication complex formation.¹²⁵ 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.¹²⁶ 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.^{126,127} 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-2.¹⁻⁴ LRRN2 has also been recently reported to interact with ORF3A and ORF7B proteins of SARS-CoV-2⁵² which have been involved in virus replication and virion assembly.^{128,129} 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.¹³⁰ Upon activation, these TLRs stimulate variety of inflammatory cytokines and interferons. TLR9 recognizes un-methylated cytosine-phosphate-guanine (CpG) dinucleotides, commonly found in bacterial and viral DNA and triggers different downstream signalling molecules to produce inflammatory cytokines and interferons.¹³⁰ The expression of TLR9 has been observed in variety of cells i.e. plasmacytoid dendritic cells, macrophages, monocytes and B lymphocytes.¹³¹ Apart from bacterial or viral infections, TLR9 is activated in several other conditions like auto-immune disease, cancer and tissue damage.¹³²⁻¹³⁴ TLR9 is not only activated during infection with bacteria and DNA viruses, RNA viruses such as influenza or dengue virus also activates TLR9 expression.^{135,136} 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.¹³⁶ Recent CRISPR-CAS9 based screenings have also identified TLR9 to be one of the host factors which are important for SARS-

CoV-2 replication.¹⁻⁴ A recently published article hypothesized that TLR9 might play a critical role in COVID-19 pathogenesis.¹³⁷ 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-2.¹³⁸ 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.¹³⁹ 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 (Figure 1). 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.¹⁴⁰ Therefore, it can be hypothesized that

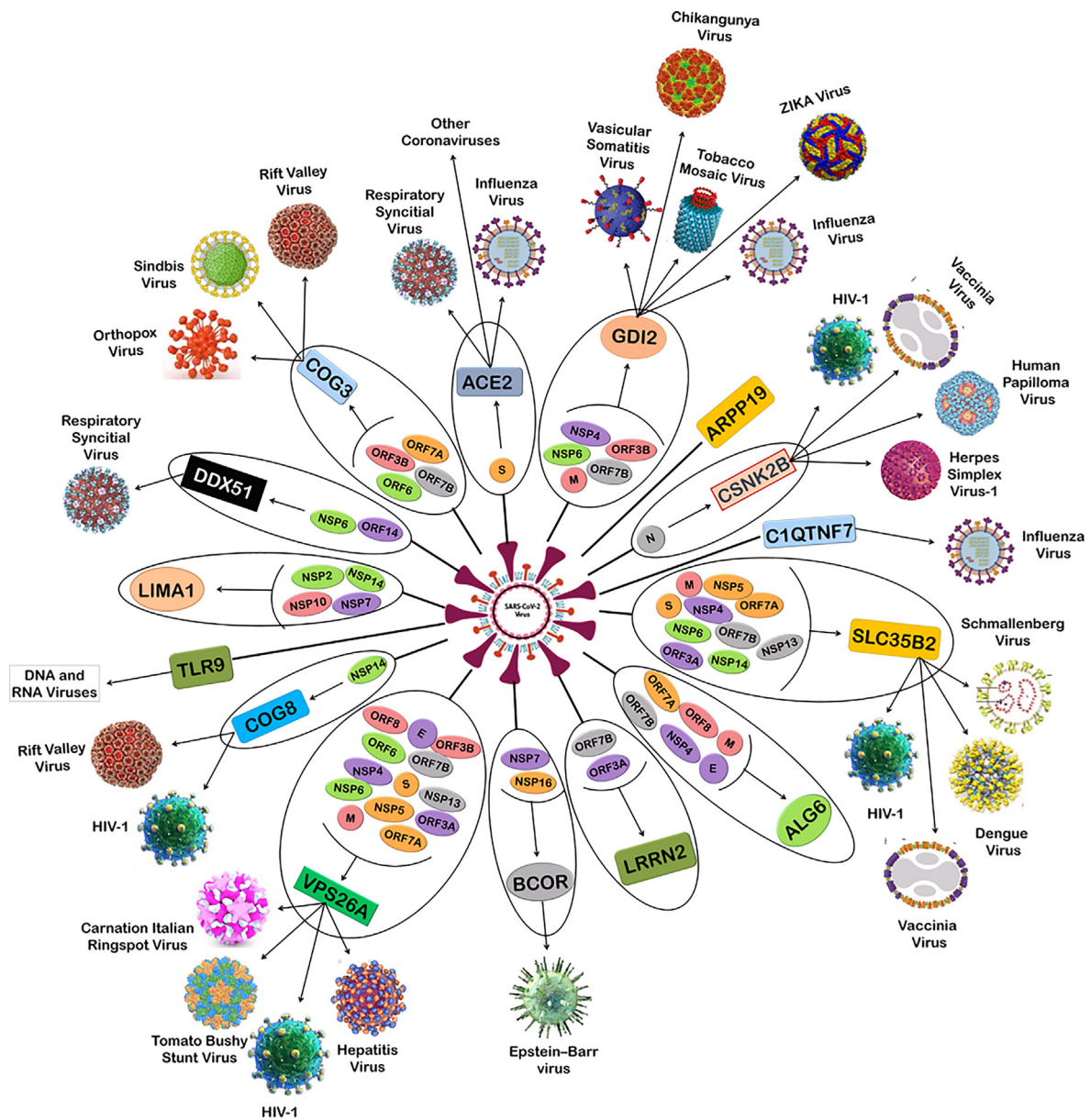


Figure 1. The fifteen host proteins (ACE2, GDI2, TLR9, VPS26A, ARPP-19, SLC35B2, COG3, COG8, ALG6, BCOR, C1QTNF7, DDX51, LRRN2, CSNK2B, LIMA1) were found to be common in at least three recently published CRISPR screening of SARS CoV-2. ACE2 protein is known to interact with viral S protein. GDI2 interacts with viral NSP4, NSP6, M, ORF3B and ORF7B proteins. SLC35B2 interacts with viral S, M, NSP 4, NSP5, NSP6, ORF3A, ORF7A, ORF7B, 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.

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.¹⁴¹

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 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.

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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. Banerjee:** Supervision, Data curation. **Vikas Sood:** Conceptualization, Supervision.

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COVID-19;
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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; CSNK2B, casein kinase 2 subunit beta; VACV, vaccinia virus; HPV, Human Papilloma Virus; HIV-1, Human Immunodeficiency Virus 1; HSV-1, Herpes Simplex Virus-1; GDI2, GDP dissociation inhibitor beta; IAV, Influenza A virus; TMV, Tobacco Mosaic Virus; VSV, Vesicular Stomatitis 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-glycosyltransferase; CDGS, 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

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