

Fig. S1. Evaluation of IC_{50} for DCLK1-IN-1 against SARS-CoV-2. (A) IC_{50} of DCLK1-IN-1 (DCLK1 kinase inhibitor) for the inhibition of SARS-CoV-2 production. The virus-infected Calu 3 cells were treated with increasing amounts of DCLK1-IN-1 and the media supernatant were used for $TCID_{50}$ assay. (B) IC_{50} for DCLK1-IN-1 against Spike expression was determined by Western blot of the infected Calu 3 cell lysates at varying concentrations of the inhibitor. The spike protein band intensities were quantitated by Image J.



Fig. S2. Strategy for the quantitative proteomic and bioinformatic analysis and the number of replicates for each group. A1 (uninfected), A2 (infected), A3 (infected and treated with DMSO), and A4 (infected and treated with DCLK1-IN-1).

A. Increased protein abundance by SARS-CoV-2 infection

A1	A2	A3	A4			
				Signal transducer and activator of transcription 1 (STAT1)		
				TryptophantRNA ligase, cytoplasmic (WARS1)		
				Gamma-enolase (ENO2)		
				Interferon-induced GTP-binding protein (MX2)		
				2'-5'-oligoadenylate synthese 2 (OAS2)		
				5'-nucleotidase (NT5C3A)		
				Putative heat shock protein HSP 90-alpha A4 (HSP90AA4P)		
				Histone H3.2 (H3C15)		
				Interferon-induced 35 kDa protein (IFI35)		
				Malignant T-cell-amplified sequence 1 (MCTS1)		
				/-methylguanosine phosphate-specific 5'-nucleotidase (NT5C3A)		
				Low molecular weight phosphotyrosine protein phosphatase (ACP1)		
				WD repeat-containing protein 75 (WDR75)		
				Dual specificity mitogen-activated protein kinase kinase 1 (MAP2K1)		
				Interferon-induced helicase C domain-containing protein 1 (IFIH1)		
				DCN1-like protein (DCUN1D1)		
				Eukaryotic peptide chain release factor GTP-binding subunit ERF3B (GSPT2)		
				AP-3 complex subunit delta-1 (AP3D1)		
				Complex I-49KD (NDUF 52) Pas suppressor protein 1 (PSI I1)		
				RAB11-binding protein RELCH (RELCH)		
				N-mvc-interactor(NMI)		
				FAS-associated death domain protein (FADD)		
				Golgi to ER traffic protein 4 homolog (GET4)		
				Galectin (LGALS9C)		
				Beta-2-microglobulin (B2M)		
				Cytosolic Fe-S cluster assembly factor NODPT (NODPT)		
				Interferon-induced protein (GETP)		
				Charged multivesicular body protein 3 (CHMP3)		
				Copine-3 (CPNE3)		
				Interferon-stimulated gene 20 kDa protein (ISG20)		
				2',5'-phosphodiesterase 12 (PDE12)		
				Thyroid recenter interacting protein 6 (TPIP6)		
				Protein Smaug homolog 2 (SAMD4B)		
				RNA helicase (DDX58)		
				Pirin (PIR)		
				Helicase SKI2W (SKIV2L)		
				Thymidine kinase(TK1)		
				Interferon-induced protein with tetratricopeptide repeats 5 (IFIT5)		
				Phosphomevalonate kinase (PMVK)		
				Phosphatidylinositol 3-kinase regulatory subunit alpha (PIK3R1)		
				Optineurin (OPTN)		
				CSC1-like protein 1 (TMEM63A)		
				Gamma-soluble NSF attachment protein (NAPG)		
				Chromosome 12 open reading frame 5(TIGAR)		
				Neurotascin (NFASC)		
				Spectrin alpha chain (SPTA1)		
				Interferon regulatory factor 2-binding protein 1 (IRF2BP1)		
				Latexin (LXN)		
				Death-associated protein kinase 3 (DAPK3)		
				Galectin-1 (LGALS1)		
				Carabin (TBC1D10C)		
				Serine protease 33 (PRSS33)		
				E3 ubiquium-protein ligase KINF31 (KINF31) Serine/threenine-protein kinase mTOR (MTOR)		
				Mediator of RNA polymerase II transcription subunit 16 (MED16)		
				EH domain-containing protein 4 (EHD4)		

B. Decreased protein abundance by SARS-CoV-2 infection

A1	A2	A3	A 4	
				Solute carrier family 12 member 2 (SLC12A2)
				HLA class I antigen (HLA-A)
				Laminin subunit beta-3 (LAMB3)
	Ĩ.			39S ribosomal protein L10 (MRPL10)
				Long-chain-fatty-acidCoA ligase 4 (ACSL4)
				39S ribosomal protein S30 (MRPS30)
	1			Polypyrimidine tract-binding protein 2 (PTBP2)
				Laminin subunit gamma-2 (LAMC2)
				Protein disulfide-isomerase A5 (PDIA5)
				Alpha-(1,6)-fucosyltransferase (FUT8)
				Uveal autoantigen with coiled-coil domains and ankyrin repeats (UACA)
				DNA-directed RNA polymerase I subunit RPA43 (POLR1F)
				Translocator protein (TSPO)
				Stearoyl-CoA desaturase (SCD)
				SAP30-binding protein (SAP30BP)
				Focal adhesion kinase 1 (PTK2)
				Spliceosome-associated protein CWC15 homolog (CWC15)
				Ribonuclease T2 (RNASET2)
				Ribosomal biogenesis protein (LAS1L)
				28S ribosomal protein S9 (MRPS9)
				Serine/threonine-protein kinase tousled-like 1 (TLK1)
				GPI transamidase component PIG-T (PIGT)
				Complex I-20kD (NDUFS7)
				Mitochondrial antiviral-signaling protein (MAVS)
				28S ribosomal protein S21 (MRPS21)
				Squalene monooxygenase (SQLE)
				Transmembrane protein 245 (TMEM245)
				Pre-mRNA-processing factor 40 nomolog A (PRPF40A)
		_		Valacyclovir hydrolase (BPHL)
				HCG19/96, ISOTORM CRA_D (KNDC1)
				Protein-tyrosine-phosphatase (DUSP18)
Min				Max
IVIIII				Ινιαλ

Fig. S3. Heat map of protein abundance in all four conditions as indicated. (A) upregulation of protein levels by SARS-CoV-2 infection (average of triplicate, red, A2 an), which were normalized by DCLK1-IN-1, green, A4) but not by vehicle (A3). (B) Infection-induced downregulated proteins (A2, green) were restored by DCLK1-IN-1 (red, A4) similar to uninfected levels (A1)





B. Clustering of phosphorylated peptides that are downregulated by SARS-CoV-2 infection





Fig. S4. Cluster analyses of the infection-induced upregulated (A) and downregulated (B) phosphorylated peptides detected during phosphoproteomic quantitation. A1 through A4 are as indicated in Fig. S3. (C) Overall status of phosphorylated proteins under all four condition. A1 (uninfected) and A4 (infected and DCLK1-IN-1 treated) cluster together whereas A2 (infected and untreated) and A3 (infected and DMSO-treated) show heightened phosphorylation of the proteins. (D and (E) Volcano plot showing relative increase (red) or decrease (green) of the phosphorylated peptides under four conditions described above.



Antibody and reagents	Cat#	Manufacturer
SARS-CoV-2 Nucleocapsid Protein (HL344) Rabbit mAb 100 μl	26369S	Cell Signaling Technology
SARS-CoV-2 Spike Protein (RBD) (E7B3E) Rabbit mAb #63847	63847S	Cell Signaling Technology
Anti-SARS spike glycoprotein antibody [1A9]	ab273433	Abcam
Anti-DCAMKL1/DCLK1 antibody [EPR6085] (ab109029)	ab109029	Abcam
Licor beta-Actin Mouse Monoclonal Antibody, 100 uL	926-42212	LI-COR Biosciences
Licor beta-Actin Rabbit Monoclonal Antibody, 100 uL	926-42210	LI-COR Biosciences
WDR75 Polyclonal Antibody	PA5-70946	Thermo Fisher Scientific
Anti-Galectin 1 antibody [EPR3206(2)] (ab138513)	ab138513	Abcam
GSPT2 Antibody	PA5-100254	Thermo Fisher Scientific
SAMD4B Antibody	NBP1-94045	Novus Biologicals
NDUFS7 Polyclonal Antibody	PA5-106367	Thermo Fisher Scientific
KNDC1 Polyclonal Antibody	BS-10056R	Thermo Fisher Scientific
TSPO Antibody (MA5-33203) in ICC/IF	MA5-33203	Thermo Fisher Scientific
HLA-A Polyclonal Antibody, Unconjugated,	PA5-29911	Thermo Scientific
SP-C (H-8)	sc-518029	Santa Cruz Biotechnology
CD206 (15-2)	sc-58986	Santa Cruz Biotechnology
Anti-Angiotensin Converting Enzyme 2 antibody (ab15348)	ab15348	Abcam
DCLK1-IN-1	7285	Tocris
DAPI ready made solution with Antifade	MBD0020-10ML	Sigma-Aldrich
New Coronavirus Nucleic Acid Detection Kit	2019-NCOV-PCR-AUS	PerkinElmer

Table S1: reagents used in this paper