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REVIEW ARTICLE

Genomics insights of SARS-CoV-2 (COVID-19) into target-based drug discovery

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Abstract

Coronavirus disease (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is a global health emergency and no clinically approved vaccines or antiviral drugs available to date. Intensive research on SARS-CoV-2 is urgently warranted to understand its pathogenesis and virulence mechanisms and to discover target-based antiviral therapeutics. Among various research logics, current bioinformatics highlights novel testable hypotheses for systematic drug repositioning and designing against COVID-19. A total of 121 articles related to bioinformatics facets of this virus were collected from the PubMed Central. The content of each investigation was comprehensively reviewed, manually curated, and included herein. Interestingly, 109 COVID-19-related literature published in 2020 (January–June) were included in this review. The present article emphasizes novel resource development on its genome structure, evolution, therapeutic targets, drug designing, and drug repurposing strategies. Genome organization, the function of coding genes, origin, and evolution of SARS-CoV-2 is described in detail. Genomic insights into understanding the structure–function relationships of drug targets including spike, main protease, and RNA-dependent RNA polymerase of SARS-CoV-2 are discussed intensively. Several molecular docking and systems pharmacology approaches have been investigated some promising antiviral drugs against SARS-CoV-2 based on its genomic characteristics, pathogenesis mechanism, and host specificity. Perhaps, the present genomic insights of this virus will provide a lead to the researchers to design or repurpose of antiviral drugs soon and future directions to control the spread of COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Genomics · Drug target · Network pharmacology · Molecular docking

Introduction

The coronavirus disease 19 (COVID-19) is a global epidemic with high morbidity and mortality. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new strain isolated from the Huanan Seafood Market, Wuhan, China in December 2019 (Fox 2020; Khan et al. 2020b). Horseshoe bat is a primary reservoir, but the intermediate source of origin and transfer to humans is fully understood (Guo et al. 2020; Singhal 2020). Human coronaviruses (*Coronaviridae* family; *Nidovirales* order) can cause respiratory, gastrointestinal, hepatic, and central nervous system diseases. SARS-CoV-2 is the seventh coronavirus of which two α-coronaviruses (HCoV-229E and HCoV-NL63) and two β-coronaviruses (HCoV-OC43 and HCoV-HKU1) are causing only mild self-limiting upper respiratory diseases. SARS-CoV-2, SARS-CoV, and MERS-CoV can cause severe diseases (Li et al. 2020a). Human-to-human contact and travel-related cases are transmission mechanisms for the SARS-CoV-2 outbreak (Ralph et al. 2020). The fecal–oral transmission is a possible transmission mechanism of SARS-CoV-2 infection in children (Zhang et al. 2020c). SARS-CoV-2 is sensitive to heat and UV rays and can be effectively destroyed with the use of 75% ethanol, *p*-acetic acid, and chlorine-containing disinfectants (Zhou et al. 2020b).

On 11 March 2020, the World Health Organization (WHO) declared the outbreak a pandemic. As of 20 July 2020, 14.6 million cases have been confirmed in more than 210 countries, with 608k deaths. The United States, Spain, Italy, and Germany have registered more cases than China,

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where the outbreak started (https://www.worldometers.info/coronavirus/). Consequently, the WHO declared a state of global health emergency to coordinate scientific and medical efforts to rapidly develop a cure for patients (Sohrabi et al. 2020). The development of more targeted inhibitors is highly desirable, but no effective antiviral drugs or vaccines available to date (Li et al. 2020b). The source of origin, transmission, and pathogenesis mechanisms of this virus are not yet known. It hampers further investigation of safe and valuable antiviral medications. The massive research works on its genomics perspectives provide a warrant to discover antivirals against COVID-19 infectivity.

Genomic insights of SARS-CoV-2

Genome structure

SARS-CoV-2 belongs to the *Sarbecovirus* subgenus (*β-Coronavirus* genus). It is an enveloped virus containing a single positive-stranded RNA (Chan et al. 2020a; Lu et al. 2020; Licastro et al. 2020; Yu et al. 2020; Zhou et al. 2020a, b). The first genome sequence (accession: NC_045512.2) was completed for SARS-CoV-2 Wuhan-Hu-1 isolated from Wuhan, Hubei province, China (Wu et al. 2020). Continuous genome sequencing attempts of different laboratories have been produced 930 GenBank sequences and 288 next-generation sequences to date. The genome size of this virus is 29.9 kb with 11 open reading frames (Orfs). ORF1ab (266–21555 nts.) encodes replicase polyprotein 1ab. After cleaved by two proteases, ORF1ab (266–13483 nts.) encodes replicase polyprotein 1a with multiple functions. Gene-coding proteins are organized as 5′-leader-UTR-replicase-ORFab-S (spike)-E (envelope)-M (membrane)-N (nucleocapsid)-3′UTR-poly (A) tail-3′-UTR end (Kandeel et al. 2020; Zhou et al. 2020a) (Table 1).

The ORF1ab gene encodes a polyprotein consisting of 15 nonstructural proteins (Nsp1-16) (Fig. 1). This polyprotein is auto-proteolytically cleaved into multiple enzymes that form replicase-transcriptase machinery consisting of RNA-dependent RNA polymerase (RdRp), helicase, 3′–5′ exonuclease, endoRNAse and 2′-O-ribose methyltransferase. These enzyme components are essential to viral genome replication and nucleic acid metabolism (Gordon et al. 2020). The replicase-transcriptase system assembles at the host endoplasmic reticulum where structural proteins assembled to make essential cellular components (capsid).

A nonstructural protein 1 (Nsp1) is a host translation inhibitor that facilitates efficient viral gene expression in infected cells and evasion from the host immune response by interacting with the 40S ribosomal subunit. ORF1ab gene contains coronavirus frameshifting stimulation element stem-loop 1 and 2 in the position of 13476–13503 and 13488–13542 nucleotides, respectively. ORF10 gene harbors coronavirus 3′ UTR pseudo-knot stem-loop 1 (29609–29644 nucleotides) and 2 (29629–29657 nucleotides). The size of the stem-loop structure is ranged from 27 to 54 nucleotides. The genomic position 29740–29758 nucleotides form a noncanonical C: T base pair. The homologous positions form a highly conserved C: G base pair (Ashour et al. 2020; Kandeel et al. 2020; Li et al. 2020d).

Genome evolution

The genome of SARS-CoV-2 is about 82%, 96%, and 86.9% identical to the SARS-CoV, bat-CoV-RaTG13, and bat-SL-CoVZC45, respectively (Zhou et al. 2020b). However, the SARS-CoV-2 genome is genetically distinct from SARS-CoV and has a relatively long branch length to the bat-CoV-RaTG13 and bat-SL-CoVZXC21. SARS-CoV-2 genome is 99.98% identical across the SARS-CoV-2 genomes obtained from different patients (Lu et al. 2020). The genome-coding potential is closely related to those of the bat, civet, and HCoVs (Chan et al. 2020a). Genetic recombination events are complex more likely occurring in bat-CoV-RaTG13 and bat-SL-CoVZXC21than in SARS-CoV-2 (Lu et al. 2020; Paraskevis et al. 2020). A phylogenetic network analysis of 160 complete SARS-CoV-2 genomes found three central mutational variants distinguished by amino acid changes. Accordingly, it has classified into A, B, and C ancestral types. The synonymous mutations T29095C and T8782C are identified in type A and type B, respectively. The non-synonymous mutations C28144T (Leu to Ser) and G26144T (Gly to Val) are detected in type B and type C, respectively (Forster et al. 2020). Therefore, the genetic diversity of SARS-CoV-2 has been expanded in human hosts due to the establishment of hyper-variable genomic hotspot its population (Wen et al. 2020).

Hyper-variable genomic hotspots

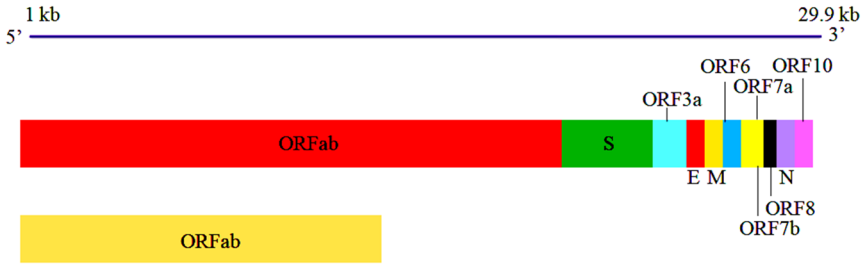
Some mutational hotspots identified from structural and nonstructural genes had deleterious effects on the functional evolution of coding proteins, host specificity, and infectivity of SARS-CoV-2 (Li et al. 2020c; Phan 2020). SARS-CoV-2 mutational hotspots are located at positions 1397, 2891, 14408, 17746, 17857, 18060, 23403, and 28881, where a mutation at position 14408 is adjacent to the drugs targeting RdRp hydrophobic clef (Pachetti et al. 2020). The spike glycoprotein of this virus contains a receptor-binding domain (RBD), which shares only a 40% amino acid identity with other SARS-related coronaviruses (Chan et al. 2020a). It has the non-synonymous mutation sites that slow down the development of therapeutics apart from biologics and macrocyclic peptides (Morse et al. 2020). The RBD has

Table 1 Genomic information of emerging SARS-CoV-2 Wuhan-Hu-1 isolate (Accession: NC_045512.2)

Locus tag	Gene	Start	Stop	Strand	Length	Protein Name	Gene ID	Protein ID
GU280_gp01	ORF1ab	266	21555	+	7096	ORF1ab polyprotein	43740578	YP_009724389.1
GU280_gp01	ORF1ab	266	13483	+	4405	ORF1a polyprotein	43740578	YP_009725295.1
GU280_gp02	S	21563	25384	+	1273	Surface glycoprotein	43740568	YP_009724390.1
GU280_gp03	ORF3a	25393	26220	+	275	ORF3a protein	43740569	YP_009724391.1
GU280_gp04	E	26245	26472	+	75	Envelope protein	43740570	YP_009724392.1
GU280_gp05	M	26523	27191	+	222	Membrane glycoprotein	43740571	YP_009724393.1
GU280_gp06	ORF6	27202	27387	+	61	ORF6 protein	43740572	YP_009724394.1
GU280_gp07	ORF7a	27394	27759	+	121	ORF7a protein	43740573	YP_009724395.1
GU280_gp08	ORF7b	27756	27887	+	43	ORF7b	43740574	YP_009725296.1
GU280_gp09	ORF8	27894	28259	+	121	ORF8 protein	43740577	YP_009724396.1
GU280_gp10	N	28274	29533	+	419	Nucleocapsid phosphoprotein	43740575	YP_009724397.2
GU280_gp11	ORF10	29558	29674	+	38	ORF10 protein	43740576	YP_009725255.1
GU280_gp01	ORF1ab	13476	13503	+	27	Coronavirus frameshifting stimulation element stem-loop 1		
GU280_gp01	ORF1ab	13488	13542	+	54	Coronavirus frameshifting stimulation element stem-loop 2		
GU280_gp11	ORF10	29609	29644	+	35	Coronavirus 3′ UTR pseudo-knot stem-loop 1		
GU280_gp11	ORF10	29629	29657	+	28	Coronavirus 3′ UTR pseudo-knot stem-loop 2		
3′UTR stem-loop motif[a]		29675	29903	+	228	Coronavirus 3′ stem-loop 2-like motif (s2m)		
		29728	29768	+	40	Coronavirus 3′ stem-loop 2-like motif (s2m)		

[a]Coordinates 29740:29758 form a noncanonical C: T base pair, but the homologous positions form a highly conserved C: G base pair in other viruses, including SARS (NC_004718.3)

(A) Genome structure of SARS-CoV-2



(B) ORF1ab gene-coding proteins

ORF1ab-coding proteins	ORF1ab polyprotein				ORF1a polyprotein			
	Start	Stop	Length	Protein ID	Start	Stop	Length	Protein ID
Leader protein	1	540	540	YP_009725297.1	266	805	540	YP_009742608.1
Nsp2	541	2454	1914	YP_009725298.1	806	2719	1914	YP_009742609.1
Papain-like protease	2455.	8289	5835	YP_009725299.1	2720	8554	5835	YP_009742610.1
Nsp4	8290	9789	1500	YP_009725300.1	8555	10054	1500	YP_009742611.1
3C-like proteinase	9790	10707	918	YP_009725301.1	10055	10972	918	YP_009742612.1
Nsp6	10708	11577	870	YP_009725302.1	10973	11842	870	YP_009742613.1
Nsp7	11578	11826	249	YP_009725303.1	11843	12091	249	YP_009742614.1
Nsp8	11827	12420	594	YP_009725304.1	12092	12685	594	YP_009742615.1
Nsp9	12421	12759	339	YP_009725305.1	12686	13024	339	YP_009742616.1
Nsp10	12760	13176	417	YP_009725306.1	13025	13441	417	YP_009742617.1
Nsp11	-	-	-	-	13442	13480	39	YP_009725312.1
RNA-dependent RNA polymerase	13177	15971	2795	YP_009725307.1	-	-	-	-
Helicase	15972	17774	1803	YP_009725308.1	-	-	-	-
3'-to-5' Exonuclease	17775	19355	1581	YP_009725309.1	-	-	-	-
EndRNAse	19356	20393	1038	YP_009725310.1	-	-	-	-
2'-O-Ribose methyltransferase	20659	21552	894	YP_009725311.1	-	-	-	-

Fig. 1 Genomic organization and gene neighborhood (**a**) of emerging SARS-CoV-2 Wuhan-Hu-1 isolate. The function of ORF1ab gene-coding proteins is presented in (**b**)

three possible mutation hotspots include D614G, G476S, and V483A of which V483A repeated more frequently followed by G476S. A variant D614G could bring a potentially crucial change in a protein sequence due to aspartic acid is a negatively charged and acidic amino acid compared to glycine (Banerjee et al. 2020).

The envelope and nucleocapsid proteins contain two evolutionarily conserved regions with a sequence identity of 89–96% to the SARS-CoV. ORF3b and ORF8 proteins are structurally different from those of SARS-CoV (Zhou et al. 2020b). The endosome-associated-protein-like domain in sp2 protein had a stabilizing mutation. The Nsp3 protein is imposed by a destabilizing mutation. It suggests a possible mechanism of differentiating SARS-CoV-2 from SARS-related coronaviruses (Angeletti et al. 2020). The hypervariable genomic hotspot (Ser/Lue) is found in ORF8 protein (Ceraolo and Giorgi 2020). The mutations identified in Nsp1, Nsp3, and Nsp15 might facilitate human adaptation and infection (Wen et al. 2020). The intrinsic disorder predisposition in the nonstructural proteins during evolution may also provide important information to explore its infectivity (Fahmi et al. 2020; Goh et al. 2020). Since, finding mutational variants in viral target proteins are important to assess possible drug-resistance phenotypes, leading to modulate the clinical presentation of the COVID-19 worldwide.

The high-frequency SNP mutation sites and hypervariable hotspots are important for designing a COVID-19 vaccine and rapid detection of different genotypes of SARS-CoV-2. Most recently, a genotypic method has been established for monitoring and tracing SARS-CoV-2 mutations (Yin 2020). The 2019 Novel Coronavirus Resource (2019nCoVR, https://bigd.big.ac.cn/ncov) was built for studies on viral taxonomy, genome evolution, molecular diagnosis, and drug development (Zhao et al. 2020). The Genome Detective Coronavirus Typing Tool has been developed for accurate tracking of new viral mutations in SARS-CoV-2 genome sequences (Cleemput et al. 2020). These resources would allow us to agitate the drug discovery process for the COVID-19 infectivity.

Pathogenomics

The functions of structural and nonstructural proteins are associating with pathophysiology and virulence of SARS-CoV-2. The envelope protein has a critical role in viral assembly and releases exerting viral pathogenicity and other nonstructural proteins have not yet been described (Wang et al. 2020b). The surface glycoprotein contains the S2 subunit comprising a fusion peptide, a transmembrane domain, and a cytoplasmic domain (Rabaan et al. 2020). These domains are guiding the link to host receptors. An in silico mutational study suggests a higher affinity of the SARS-Cov-2 spike protein favorable to the human ACE2 receptor, compared to the Bat-CoV spike protein (Hussain et al. 2020; Ortega et al. 2020). The N82 in ACE2 is closer contact with spike protein than M82 in human ACE2 (Luan et al. 2020). Structural genomics analysis on spike protein provides important insights to design an optimized ACE2 for SARS-CoV-2 infection. The structural variations in spike protein (Ser19Pro; Glu329Gly) and the transmembrane helical segments of nsp2 and nsp3 proteins (Ser723Gly; Pro1010Iso) may determine the host specificity of SARS-CoV-2. Such mutation hotspots in spike protein and nonstructural proteins of SARS-CoV-2 might affect molecular recognition and specificity of antivirals or vaccigenic candidates. These mutations can also influence the binding efficiency of PCR primers or probes during the molecular diagnosis of clinical samples. Consequently, evidence of such mutation hotspots could explain how SARS-CoV-2 has a mechanism for disease relapses in a host (Angeletti et al. 2020; Korber et al. 2020).

SARS-CoV-2 infection is capable of producing an excessive immune reaction in the host. The IL-6 is produced during infection by activated leukocytes and acts on a large number of cells and also stimulates the production of acute-phase proteins important to the thermoregulation. Subsequently, B lymphocyte differentiation has been elevated for inhibition of further virus replication in a host (Cascella et al. 2020; Prompetchara et al. 2020; Rabaan et al. 2020). SARS-CoV accessory protein ORF6 antagonizes the antiviral activity of the STAT1 transcription factor by sequestering IMPα/β1 on the rough ER/Golgi membrane (Frieman et al. 2007). Ivermectin is the US Food and Drug Administration (FDA)-approved broad-spectrum antiparasitic agent and HIV-1 integrase, which reported as an effective nuclear transport inhibitor against SARS-CoV-2 in vitro (Caly et al. 2020). The density of the expression levels of ACE2 in neurological tissue also suggests the possible contribution of neurological tissue damage to the morbidity and mortality caused by COIVD-19 (Baig et al. 2020).

SARS-CoV-2 requires host cellular factors for successful replication during infection. The mechanisms of its infection can be elucidated with a systematic analysis of virus-host protein–protein interactions (PPIs) (Bösl et al. 2019; Rothan and Byrareddy 2020). It is hypothesized that a host protein that functionally associates with this virus is localized in the corresponding sub-network within the comprehensive human interactome network. The host dependency factors mediating virus infection and effective molecular targets should be identified for developing broad-spectrum antiviral drugs for COVID-19. The previous virus-host proteome interaction studies identified the key host-specific proteins and interactions pathways including DNA replication, epigenetic and gene expression regulators, vesicle trafficking, lipid modification, ubiquitin ligases, and nuclear transport machinery (Table 2). Orf10 of SARS-CoV-2 has interacted with the human ubiquitin system with multiple members of the Culin-2 E3 Ligase complex (Gordon et al. 2020).

Table 2 SARS-CoV-2 proteins and human proteome interactive pathways

SARS-CoV-2 proteins	Human proteome interactive pathways
Nsp1	DNA replication
Nsp5, Nsp8, Nsp13, E	Epigenetic and gene expression regulators
Nsp6, Nsp7, Nsp10, Nsp13, Nsp15, Orf3a, E, Orf8	Vesicle trafficking
Spike	Lipid modification
Nsp8, N	RNA processing and regulation
Orf10	Ubiquitin ligases
Nsp8, Nsp13, N, Orf9b	Host signaling
Nsp9, Nsp15, Orf6	Nuclear transport machinery
Nsp1, Nsp13	Cytoskeleton
Nsp4, Nsp8, Orf9c	Mitochondria
Nsp9	Extracellular matrix

Source: Gordon et al. (2020)

Structural genomics on drug targets

Structural genomics analysis reveals the SARS-CoV-2 genome consisting of four structural proteins (S–E–M–N) and two nonstructural proteins (main protease and RdRp) (Kandeel et al. 2020). Spike, main protease (3CLpro), papain-like protease (PLpro), and RdRp are promising therapeutic targets for SARS-CoV infections (Li and De Clercq 2020; Yoshimoto 2020). The structural and functional characteristics of these proteins are summarized here and represented in Table 3. Viral exoribonuclease greatly affects the cell's transcriptome by RNA processing and degradation.

Spike glycoprotein

SARS-CoV-2 infects ciliated bronchial epithelial cells and type-II pneumocytes where an envelope-anchored spike protein binds to a host receptor angiotensin-converting enzyme 2 (ACE2) (Lan et al. 2020; Li et al. 2020e; Zhou et al. 2020a). The spike protein is cleaved via acid-dependent proteolysis by furin protease into an N-terminal S1 subunit (residue 14–685) and a C-terminal S2 region (residue 686–1273), followed by fusion of the viral envelop to the cellular membranes (Coutard et al. 2020). It has a functional polybasic (furin) cleavage site at the S1–S2 boundary through the insertion of 12 nucleotides. Both the polybasic cleavage site and the three adjacent predicted O-linked glycans are unique to SARS-CoV-2. Insertion of a furin cleavage site at the S1–S2 junction enhances cell–cell fusion without affecting viral entry (Hasan et al. 2020; Rabaan et al. 2020; Walls et al. 2020).The function of the predicted O-linked glycans could create a 'mucin-like domain' that helps SARS-CoV-2 to utilize mucin-like domains as glycan shields involved immunoevasion (Bagdonaite and Wandall 2018).

Crystallographic studies reveal the structure of the six-helical bundle core of the HR1 and HR2 domains in the S2 subunit (Fig. 2). It has a defined RBD in an N-terminal S1 subunit that specifically recognizes its receptor in humans (Lan et al. 2020; Lu et al. 2020; Xia et al. 2020). The RBD contains a core structure and a receptor-binding motif (RBM) that binds to the ACE2 receptor-binding region, integrin (Cagliani et al. 2020; Sigrist et al. 2020). The involvement of glucose-regulated protein-78 and RBD are important in recognition of the host ACE2 receptor. The binding is more favorable between regions III (C391–C525) and IV (C480–C488) of the spike protein and glucose-regulated protein-78 (Ibrahim et al. 2020).

The binding efficiency of RBD on ACE2 can be enhanced by the presence of specific amino acids at the 442, 472, 479, 480, and 487 positions. Gln493 and Asn501 residues in the RBM provide possible interactions with ACE2. SARS-CoV-2 has acquired some capacity for human cell infection and human-to-human transmission by super binding affinity of Gln493 and Asn501 residues in RBM with ACE2 (Wan et al. 2020). It is most likely the result of natural selection on a human (Andersen et al. 2020; Zhang et al. 2020a).

The RBM recognizes directly the integrins of the ACE2 receptor-binding region and RBD has a critical impact on the cross-reactivity of neutralizing antibodies. It suggests a promising therapeutic target. EK1C4 is the most potent pan-coronavirus fusion inhibitor targeting its spike protein (Xia et al. 2020). ACE2 blocker is repurposed to control COVID-19 from gaining entry into the host cell (Phadke and Saunik 2020). Therefore, it is still necessary to develop novel monoclonal antibodies targeting RBD and fusion inhibitors targeting the S2 subunit, which will be effective therapeutics against COVID-19 (Sigrist et al. 2020; Shanmugaraj et al. 2020; Tian et al. 2020).

RNA-dependent RNA polymerase

The RdRp is a crucial viral enzyme in the life cycle of RNA viruses that catalyzes the replication of RNA from the RNA template. ORF1ab gene-encoding polyprotein can be cut by the main protease of the virus to form RdRp and helicase (Yang and Wang 2020). The structural genomics studies found the active site of this enzyme highly conserved with two successive and surface-accessible aspartates in a beta-turn structure (Elfiky 2020a, 2020b). It has conserved polymerase motifs A–G in the palm domain having an active site chamber. It has a unique N-terminal β-hairpin at its N-terminal (Gao et al. 2020b). Crystallographic structure (PDB ID: 6M71) and homology model of this enzyme offer

Table 3 Crystallographic structures information on anti-SARS-CoV-2 drugs targeting proteins

Name of protein's structure	PDB ID	Release date	Resolution (Ã)	Residue
3C-like protease (apo)	6M2Q	15-04-2020	1.7	306
3C-like protease-5,6,7-trihydroxy-2-phenyl-4H-chromen-4-one	6M2N	15-04-2020	2.198	1224
3C-like proteinase-K36	6WTJ	20-05-2020	1.9	306
3C-like proteinase-UED	6WTK	20-05-2020	2	306
Main protease	7BRO	13-05-2020	2	307
Main protease (structural plasticity)	6WQF	06-05-2020	2.3	306
Main protease (apo)	6M03	11-03-2020	2	306
Main protease (free)	6Y2E	04-03-2020	1.75	306
Main protease (monoclinic)-alpha-ketoamide 13b	6Y2F	04-03-2020	1.95	306
Main protease (orthorhombic)-alpha-ketoamide 13b	6Y2G	04-03-2020	2.2	612
Main protease (reaction state)-alpha-ketoamide 13b	6Y7M	18-03-2020	1.9	306
Main protease (unliganded active site)	6Y84	11-03-2020	1.39	306
Main protease (unliganded active site)	6YB7	25-03-2020	1.25	306
Main protease-11a	6LZE	29-04-2020	1.505	306
Main protease-11b	6M0K	29-04-2020	1.504	307
Main protease-2-Methyl-1-tetralone	6YNQ	29-04-2020	1.8	306
Main protease-AZD6482.	6YVF	20-05-2020	1.6	306
Main protease-Boceprevir	6WNP	06-05-2020	1.443	306
Main protease-Carmofur	7BUY	29-04-2020	1.6	306
Main protease-GC376	7BRR	13-05-2020	1.4	614
Main protease-GC-376	6WTT	20-05-2020	2.15	930
Main protease-HU5	7BRP	13-05-2020	1.8	614
Main protease-Leupeptin	6YZ6	20-05-2020	1.7	310
Main protease-N3	6LU7	05-02-2020	2.16	312
Main protease-N3	7BQY	22-04-2020	1.7	312
Main protease-Pyrithione zinc	6YT8	06-05-2020	2.05	306
Main protease-X77	6W63	25-03-2020	2.1	306
NSP10-NSP16 complex	6W75	25-03-2020	1.951	886
NSP10-NSP16 methyltransferase-Sinefungin	6YZ1	13-05-2020	2.4	422
NSP15 Endoribonuclease	6VWW	04-03-2020	2.2	742
NSP15 Endoribonuclease-Citrate	6W01	11-03-2020	1.9	742
NSP15 Endoribonuclease-Tipiracil	6WXC	20-05-2020	1.85	700
NSP15 Endoribonuclease-Uridine-5′-Monophosphate	6WLC	29-04-2020	1.82	700
NSP16–NSP10 complex	6W4H	18-03-2020	1.8	443
NSP16 and NSP10 methyltransferase-stimulatory factor complex	6W61	25-03-2020	2	439
NSP16–NSP10 ternary complex	6WKS	06-05-2020	1.8	437
NSP16–NSP10 heterodimer-7-Methyl-GpppA and S-adenosyl-L-homocysteine	6WQ3	06-05-2020	2.1	443
NSP16–NSP10 heterodimer-7-Methyl-GpppA and S-adenosyl-L-homocysteine	6WRZ	13-05-2020	2.25	443
NSP16–NSP10 heterodimer-7-Methyl-GpppA and S-Adenosylmethionine	6WVN	13-05-2020	2	443
NSP16–NSP10 heterodimer-S-Adenosyl-L-homocysteine	6WJT	22-04-2020	2	886
NSP16–NSP10 heterodimer-Sinefungin	6WKQ	29-04-2020	1.98	886
NSP3 ADP-ribose phosphatase	6VXS	04-03-2020	2.03	340
NSP3 ADP-ribose phosphatase (apo)	6WEN	15-04-2020	1.35	170
NSP3 ADP-ribose phosphatase-ADP-ribose	6W02	11-03-2020	1.5	340
NSP3 ADP-ribose phosphatase-AMP	6W6Y	25-03-2020	1.451	340
NSP3 ADP-ribose phosphatase-MES	6WCF	15-04-2020	1.065	170
NSP3 Macro X domain	6WEY	29-04-2020	0.95	172

Table 3 (continued)

Name of protein's structure	PDB ID	Release date	Resolution (Ã)	Residue
NSP3 macrodomain-ADP-ribose	6WOJ	06-05-2020	2.2	704
NSP3 macrodomain-ADP-ribose	6YWL	06-05-2020	2.5	865
NSP3 macrodomain-HEPES	6YWK	06-05-2020	2.2	865
NSP3 macrodomain-MES	6YWM	06-05-2020	2.16	519
NSP7 and NSP8 C-terminal domain-Cofactor complex	6WIQ	22-04-2020	2.85	208
NSP7 and NSP8 C-terminal domain-Cofactor complex	6WQD	06-05-2020	1.95	416
NSP7 and NSP8 C-terminal domain-Cofactor complex	6WTC	13-05-2020	1.85	416
NSP7-NSP8 complex	6YHU	29-04-2020	2	376
NSP9 RNA-binding protein	6W4B	18-03-2020	2.95	234
NSP9 RNA-replicase	6WXD	20-05-2020	2	232
NSP9 RNA-replicase-peptide	6W9Q	08-04-2020	2.05	133
Nucleocapsid phosphoprotein	6VYO	11-03-2020	1.7	512
Nucleocapsid phosphoprotein C-terminal dimerization domain	6WJI	22-04-2020	2.052	726
Nucleocapsid phosphoprotein C-terminal dimerization domain	6YUN	20-05-2020	1.44	270
Nucleocapsid phosphoprotein RNA-binding domain (monoclinic)	6WKP	29-04-2020	2.67	512
Nucleocapsid protein C-terminal domain	7C22	20-05-2020	2	480
Nucleocapsid protein N-terminal RNA-binding domain	6M3M	18-03-2020	2.7	544
ORF7A accessary protein	6W37	29-04-2020	2.9	67
Papain-like protease	6W9C	01-04-2020	2.7	951
Papain-like protease C111S mutant	6WRH	06-05-2020	1.6	318
Papain-like protease C111S mutant-mISG15	6YVA	13-05-2020	3.18	476
Papain-like protease-VIR250	6WUU	20-05-2020	2.79	1324
Papain-like protease-VIR251	6WX4	20-05-2020	1.655	331
Spike protein S2 subunit (post fusion core)	6LXT	26-02-2020	2.9	792
Spike protein HR2 domain	6LVN	26-02-2020	2.47	144
Spike protein RBD-ACE2	6VW1	04-03-2020	2.68	1628
Spike protein RBD-ACE2	6LZG	18-03-2020	2.5	805
Spike protein RBD-ACE2	6M0J	18-03-2020	2.45	832
Spike protein RBD-CR3022 Fab	6W41	25-03-2020	3.084	674
Spike protein RBD-CR3022 Fab	6YLA	15-04-2020	2.42	1324
Spike protein RBD-CR3022 Fab (crystal form)	6YM0	29-04-2020	4.36	661
Spike protein RBD-VHH-72 Fab	6WAQ	01-04-2020	2.2	636
Spike protein S2 subunit RBD-B38 Fab	7BZ5	13-05-2020	1.84	669

a way to find efficient RdRp inhibitors to treat COVID-19 (Elfiky 2020a) (Fig. 3). Molecular docking studies found theaflavin as a potential RdRp inhibitor that binds to the catalytic pocket of RdRp (−9.11 kcal/mol) (Lung et al. 2020). Hydrophobic and π-cation interactions are contributed significantly to binding between theaflavin and Arg553 side chain of RdRp (Lung et al. 2020). Several rapid drug repurposing efforts have been made for the identification of promising antiviral drugs (Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir) against COVID-19 (Elfiky 2020b; Gordon et al. 2020; Reina 2020; Shah et al. 2020; Wang et al. 2020a). Hence, drug repurposing strategy is an effective one to discover the FDA-approved drugs targeting RdRp.

Papain-like protease

This enzyme helps to assemble a virally induced cytoplasmic double-membrane vesicle along with Nsp4 and then cleaves at the N-terminus of the replicase polyprotein for viral replication. It also removes ubiquitin and IFN-stimulated gene 15 from cellular proteins through the processing of Lys-48- and Lys-63-linked polyubiquitin chains (Clasman et al. 2020). It can be antagonized IFN-I induced

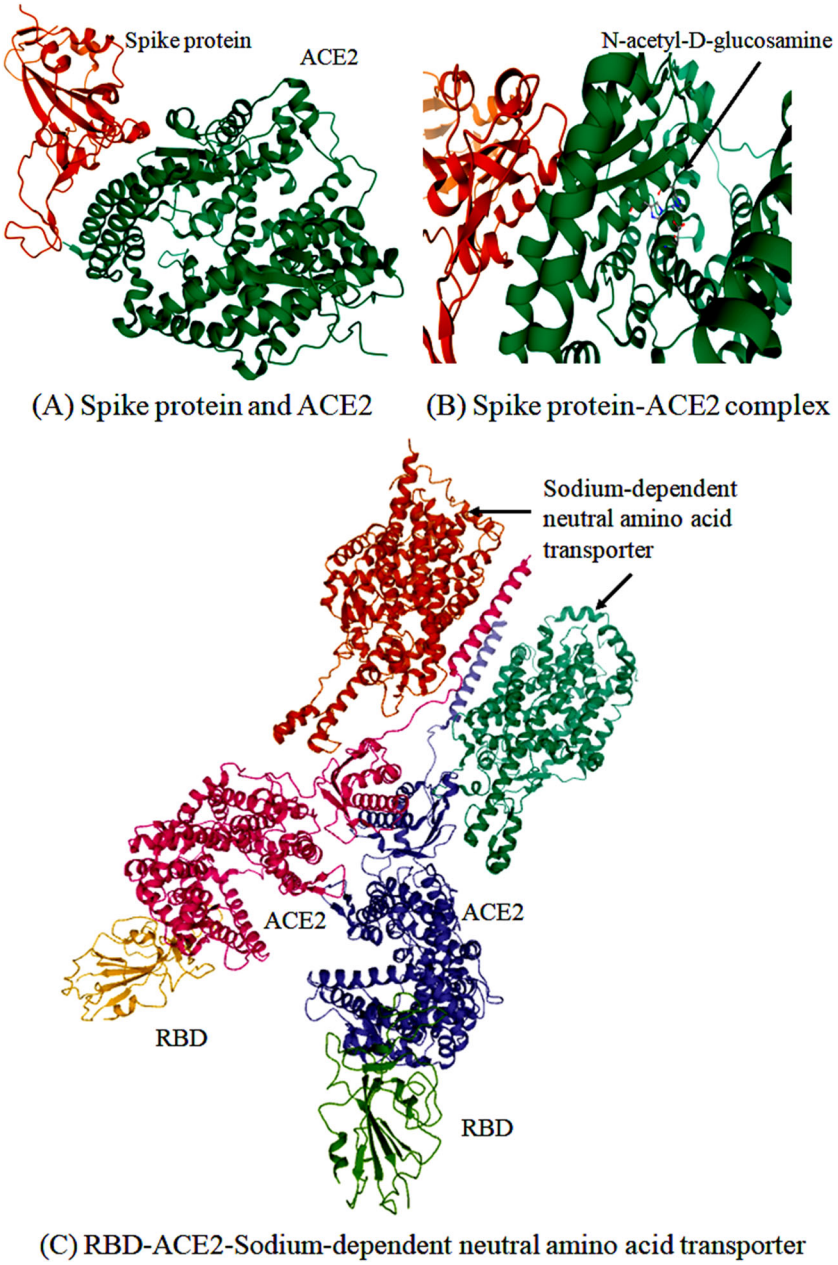


Fig. 2 3D structural view for the representation of SARS-CoV-2 spike glycoprotein (**a**) in complex with ACE2 (**b**) and sodium-dependent neutral amino acid transporter (**c**)

innate immunity and also prevented host NF-kappa-B signaling by blocking subsequent nuclear translocation of host IFN regulatory factor-3. The structural information of this enzyme provides new insights as a valuable target for drug repositioning to treat SARS-CoV-2 infections (Wu et al. 2020). Some potential inhibitors targeting papain-like protease are identified by using a virtual screening approach using the CDOCKER program (Ma et al. 2020).

Main protease

The main protease (3CL-PRO) is a cysteine protease responsible for the processing of ORF1ab polyprotein at 11 sites. It recognizes a motif sequence [ILMVF]-Q-[SGACN] in the ORF1ab polyprotein and also binds an ADP-ribose-1-phosphate moiety. As shown in Fig. 3, a crystal structure of this enzyme contains six-stranded anti-parallel β-barrels harboring a substrate-binding site located between chymotrypsin-3C protease-like domains I and picornavirus 3C protease-like domains II (Zhang et al. 2020b). Like SARS-CoV, a globular cluster of five helices is located in domain III (residues 198–303) regulating the dimerization process through a salt-bridge interaction between Glu290 of one protomer and Arg4 of the other (Shi and Song 2006; Chen et al. 2020; Chatterjee et al. 2020). Covalent main protease inhibitors are targeting the catalytic

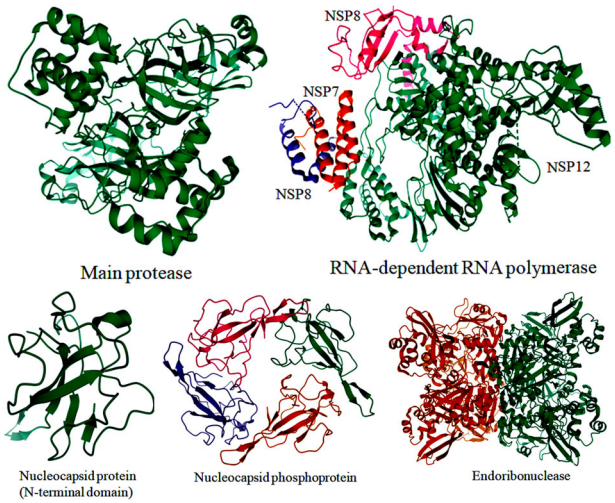


Fig. 3 3D structural view for the representation of SARS-CoV-2 proteins targeting for drug designing process

dyad (His41 and Cys145) of this enzyme (Paasche et al. 2014; Li et al. 2020c). The α-ketoamide 13b, the main protease inhibitor binds to the shallow substrate-binding site. A thiohemiketal is formed in a reversible reaction through the nucleophilic attack of the catalytic Cys145 onto the α-keto group of α-ketoamide 13b (Zhang et al. 2020b).

Several inhibitors include paritaprevir, raltegravir, velpatasvir, ledipasvir, vinyl sulfone, lopinavir, and ritonavir are identified as repurposable drugs for inhibiting 3C-like protease of SARS-CoV-2 (Chen et al. 2020; Cao et al. 2020; Morse et al. 2020; Nutho et al. 2020; Khan et al. 2020a). The FDA has already approved these antivirals for the systematic treatment of chronic hepatitis C virus and human immunodeficiency virus infections (De Clercq and Li 2016). Jeon et al. (2020) have screened and identified two FDA-approved drugs such as niclosamide and ciclesonide against SARS-CoV-2. However, no structural based inhibitors against SARS-CoV-2 infection are not yet completed a clinical trial to date (Li et al. 2020c; Liu et al. 2020a; Xu et al. 2020b).

Helicase

SARS-CoV-2 helicase is an Mg^{2+}-dependent enzyme with a zinc-binding domain in N-terminus displaying RNA and DNA duplex-unwinding activities with 5′–3′ polarity. The putative recombination patterns identified in helicase of SARS-CoV-2 are important for evolutionary survival allowing for genotype adjustment and adaptations in rapidly changing environments (Rehman et al. 2020). Helicase is considered a better choice for the development of molecular diagnostic kits than antivirals (Chan et al. 2020b; Prajapat et al. 2020).

Exoribonuclease

The nonstructural protein Nsp15 encodes a nidoviral uridylate-specific endoribonuclease (NendoU). Like other coronaviruses, it plays an important role in viral infection and pathogenesis by interacting with the Nsp7/Nsp8 complex (Zhang et al. 2018). The high-resolution crystal structure of endoribonuclease Nsp15/NendoU from SARS-CoV-2 was solved and described its catalytic domain and binding sites, which provide structural and functional evidence for developing antiviral drugs (Kim et al. 2020).

2′-O-Methyltransferase

The nonstructural protein Nsp16 encodes cap-specific mRNA 2′-O-methyltransferase responsible for the RNA cap formation and methylation process of SARS-CoV-2. It binds to the N7-methyl guanosine cap and methylates the ribose 2′-O position of the first and second nucleotide of viral mRNA, which is essential to evade the immune system. Dolutegravir and bictegravir are important inhibitors of 2′-O-ribose methyltransferase identified by using molecular docking simulations (Khan et al. 2020a).

Envelope protein

Envelope protein from SARS-CoV-2 acts as a viroporin and self-assembles in host membranes forming ion channels. Envelope protein plays a central role in virus morphogenesis and assembly. It also induces apoptosis and IL-1β overproduction in the host cells, leading to pathogenesis. The envelope protein of SARS-CoV-2 is evolutionarily conserved with higher gene expression efficiency in the hosts (Kandeel et al. 2020; Zhou et al. 2020b). Generally, viral envelope proteins act as therapeutic targets for vaccine designing and engineering.

Nucleocapsid protein

The helical nucleocapsid interacts with spike, envelope, and membrane proteins to form the assembled virion (Zumla et al. 2016). The N-terminal RNA-binding domain of nucleocapsid protein (PDB ID: 6M3M) was purified and the crystallographic structure solved for further target-based drug discovery (Fig. 3). The structure, as well as the function of this protein, was studied and then tested its interaction with various phytochemicals for identification suitable drug candidates (Gupta et al. 2020). Still, more study on this target is needed for further drug discovery to treat COVID-19.

Table 4 Anti-SARS-CoV-2 drugs and their mechanisms (approved by the World Health Organization on March 15, 2020)

Approved drug	CAS	Mechanism	Rationale for use	References
Chloroquine	54-05-7	RdRp and ACE2 cellular receptor inhibitor	Preclinical data on in vitro activity against SARS-CoV-2	Gao et al. (2020a)
Hydroxychloroquine	118-42-3	RdRp inhibitor	Preclinical data on in vitro activity against SARS-CoV-2	Wang et al. (2020a)
Lopinavir; Ritonavir	192725-17-0; 155213-67-5	M^{pro} inhibitor	An open-label trial involving hospitalized patients with confirmed SARS-CoV-2	Cao et al. (2020)
Remdesivir	1809249-37-3	RdRp inhibitor	Preclinical data on in vitro activity against SARS-CoV-2	Wang et al. (2020a)
Azithromycin	83905-01-5	Downregulation of immune responses and cytokine production	Preclinical data on in vitro activity against SARS-CoV-2	Arabi et al. (2019)
Tocilizumab	375823-41-9	IL-6 receptor inhibitor	Clinical data against SARS-CoV-2	Xu et al. (2020a)
COVID-19 convalescent plasma	–	Antibodies against SARS-CoV-2	Clinical data against SARS-CoV-2	FDA

Development of anti-SARS-CoV-2 drugs

Among therapeutic strategies, systemic corticosteroids and unselective or inappropriate administration of antibiotics for the treatment of COVID-19 are not recommended. There is no promising antiviral treatment is currently available. The WHO has approved several medications for the treatment of COVID-19 patients (Wang et al. 2020a) (Table 4). They are: lopinavir/ritonavir, chloroquine, hydroxychloroquine, and α-interferon. The development of antivirals that specific to the SARS-CoV-2 is more effective for the current treatment of the COVID-19 pandemic. Molecular modeling studies have been predicted the protein's structures from SARS-CoV-2 and also identified numerous antivirals (Cortegiani et al. 2020; Nabirotchkin et al. 2020; Ghosh et al. 2020). The constructed structural genomics and interactomics roadmaps could describe the molecular mechanisms behind the viral infection to design a vaccine or antivirals against COVID-19 (Srinivasan et al. 2020). Current knowledge of the SARS-CoV-2 genomic information will thus advance the further development of anti-SARS-CoV-2 drugs.

Structure-based drug designing

Conventional docking is a too computationally expensive and slow process for structure-based drug designing (Chellapandi and Prisilla 2018; Prathiviraj et al. 2019; Bharathi and Chellapandi 2019; Prathiviraj and Chellapandi 2020b). To address this challenge, a deep docking platform has been developed for the accelerated screening of large chemical libraries, consisting of billions of entities (Liu et al. 2020c; Ton et al. 2020). This platform utilizes quantitative structure–activity relationship models to screen out the top 1000 compounds targeting the main protease of which ZINC000541677852 predicted as a potent SARS-CoV-2 protease inhibitor (docking score −11.32 kcal/mol). Hydroxychloroquine is reported as a safe and effective drug against SARS-CoV-2 infection in vitro. Molecular docking combined with the physiologically based pharmacokinetic models has been used to identify its anti-SARS-CoV-2 activity (Yao et al. 2020). Hydroxychloroquine can also significantly inhibit the main protease and also decrease the production of cytokines during SARS-CoV-2 infection (Kandeel and Al-Nazawi 2020; Liu et al. 2020b). The crystal structures of SARS-CoV-2 main protease in complex with a SARS-CoV-inhibitor N3 and a potent broad-spectrum non-covalent inhibitor X77 were solved and deposited in the protein databank (PDB ID: 6LU7; 6W63). A docking view of the interaction between inhibitors (N3 and X77) and SARS-Cov-2 main protease is depicted in Fig. 4a.

Structure-based vaccine designing

The structural and functional characterization of spike glycoprotein, polyprotein, envelope protein, and nucleocapsid protein is important for vaccine development. A crystal structure of the SARS-CoV-2 RBD in complex with human antibody CR3022 (PDB ID: 6W41) was solved recently, which guides vaccine designing or epitope engineering for COVID-19 (Fig. 4b). The immunoinformatics approach was used to identify significant cytotoxic T lymphocyte and B cell epitopes in the SARS-CoV-2 surface glycoprotein, which facilitates vaccine design of high priority (Baruah and Bose 2020; Grifoni et al. 2020). A similar approach has been applied to propose a specific synthetic vaccine epitope and peptidomimetic agent against SARS-CoV-2 based on the sequence motif KRSFIEDLLFNKV and surrounding variations (Robson 2020).

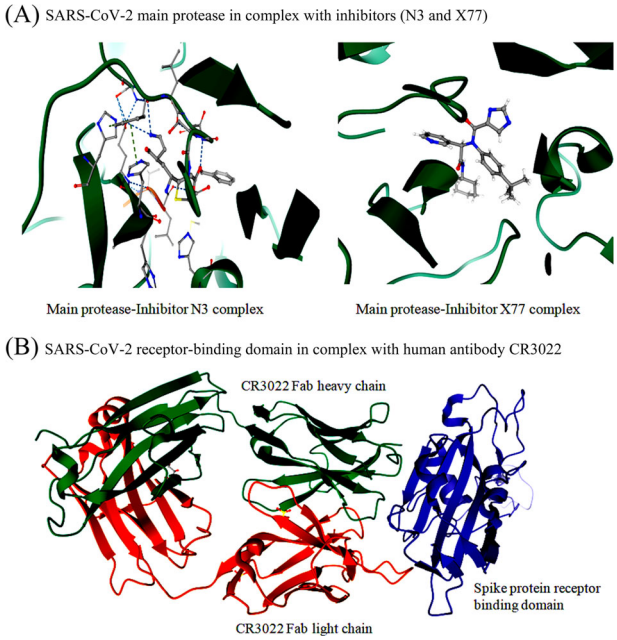


Fig. 4 3D structural view for the representation of SARS-CoV-2 target proteins in complex with main protease inhibitors (**a**) and human antibody CR3022 (**b**). The target protein is represented as a cartoon model (green) and inhibitors are represented as a ball and stick model

Systems pharmacology for drug repurposing

Systems biology offers considerable promise in uncovering novel pathways by which microbial pathogens interact with host PPI networks to mediate disease severity (Chellapandi et al. 2019; Murugan et al. 2019; Prathiviraj and Chellapandi 2020a). Systems pharmacology attempts to model the effects of drug action by simultaneously modulating multiple proteins in a network. This approach can identify cellular antiviral targets from virus-host PPIs for the development of effective treatments for viral infections. The drug-gene-metabolism-disease network models are used to identify effective repurposable drugs and drug combinations for viral infections by quantification of the interplay between the virus-host interactome and drug targets in the human PPIs network. The potential drug combination is rationally predicted from the topological relationship between two drug-target modules that reflects biological and pharmacological relationships. The suitable drug targets and repurposed drugs are evaluated with molecular docking and validated with drug-induced gene signatures and virus-induced transcriptomics in human cell lines. Thus, drug repurposing comes into sight as a novel drug discovery process to yield efficient therapies against COVID-2019 rapidly due to time consuming, safety profiles, clinical trials, and FDA approvals of newly discovery drugs (Ahn et al. 2020; Ke et al. 2020; Tu et al. 2020).

Several repurposed drugs have already been tested against COVID-2019 (Harrison 2020). Systems pharmacology-based network medicine platform has been developed for the identification of disease-related genes, whether using genomic data and expression data or data directly collected from the scientific literature (Fu et al. 2020; Zhou et al. 2020a). It is also used for the rapid identification of candidate repurposable drugs and potential drug combinations targeting SARS-CoV-2 using disease-related molecular networks. A systematic drug repurposing approach has been developed to identify promising inhibitors (Raltegravir, Paritaprevir, Bictegravir, and Dolutegravir) against 3C-like protease and 2′-O-ribose methyltransferase from SARS-CoV-2 (Khan et al. 2020a). The SCAR protocol has been developed to repurpose 6 covalent drugs targeting the main protease (3CLpro) of SARS-CoV-2 (Liu et al. 2020c). The proteomic-chemoinformatic approach has been developed for the detection of 66 druggable human proteins or host factors targeted by 69 existing FDA-approved drugs or compounds being investigated (Gordon et al. 2020).

Conclusions

The outbreak of COVID-19 poses a serious threat to global public health and local economies. The future evolution, adaptation, and spread of this virus warrant urgent investigation. It is imperative to discover affordable drugs to control and diminish the pandemic. The present review will provide new insights for those drugs currently ongoing clinical studies and also possible new strategies for drug designing or repositioning to treat SARS-CoV-2 infections. Compared to de novo drug discovery and randomized clinical trials, drug repurposing strategy could significantly shorten the time and reduce the cost of antiviral drugs. Nevertheless, experimental approaches for drug repurposing are costly and time consuming. It can be resolved by systems pharmacology approaches because targeting single virus proteins often has a high risk of drug resistance by the rapid evolution of virus genomes. Perhaps, the repositioning of launched or even failed drugs to viral diseases will provide unique translational opportunities. Genome-scale systems biological perspective of SARS-CoV-2-host interactions can guide the further in vitro and in vivo clinical studies on validation of newly identified drugs for COVID-19 infectivity. Genomic insights into developing and deploying drugs of antiviral drugs for COVID-19 will offer a substantially higher probability of success to the market and a significantly reduced cost and timeline to clinical availability. The currently established animal models are not very promising for the studies of pathogenesis and treatment of COVID-19 and therefore, testing the drugs for COVID-19 requires suitable animal models before their use in humans.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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