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Reviw article

COVID-19 signalome: Potential therapeutic interventions

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ABSTRACT

The COVID-19 pandemic has triggered intensive research and development of drugs and vaccines against SARS-CoV-2 during the last two years. The major success was especially observed with development of vaccines based on viral vectors, nucleic acids and whole viral particles, which have received emergent authorization leading to global mass vaccinations. Although the vaccine programs have made a big impact on COVID-19 spread and severity, emerging novel variants have raised serious concerns about vaccine efficacy. Due to the urgent demand, drug development had originally to rely on repurposing of antiviral drugs developed against other infectious diseases. For both drug and vaccine development the focus has been mainly on SARS-CoV-2 surface proteins and host cell receptors involved in viral attachment and entry. In this review, we expand the spectrum of SARS-CoV-2 targets by investigating the COVID-19 signalome. In addition to the SARS-CoV-2 Spike protein, the envelope, membrane, and nucleoprotein targets have been subjected to research. Moreover, viral proteases have presented the possibility to develop different strategies for the inhibition of SARS-CoV-2 replication and spread. Several signaling pathways involving the renin-angiotensin system, angiotensin-converting enzymes, immune pathways, hypoxia, and calcium signaling have provided attractive alternative targets for more efficient drug development.

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1. Introduction

The pandemic of SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2) has resulted in more than 641 million infected patients and has caused more than 6.6 million deaths worldwide since its outbreak in late 2019 [1]. In the early phase of the COVID-19 pandemic neither drugs nor vaccines against SARS-VoV-2 were available. A race against time including the development of novel and repurposed antiviral drugs and vaccines commenced, resulting in some breakthrough, especially regarding COVID-19 vaccines [2]. However, there is still room for the development of more efficient drugs and vaccines against COVID-19 not the least because of the emerging novel SARS-CoV-2 variants, which have seriously compromised the potency of existing drugs and vaccines.

Signalosomes, a large supramolecular protein complex that can cluster or oligomerize, play an important role in SARS-CoV-2 infectivity and can also provide potentially interesting therapeutic targets for antiviral drugs against COVID-19. Due to the critical impact the COVID-19 signalosome has on both viral transmission and immune evasion, alternative therapeutic opportunities might be revealed. Although SARS-CoV-2 shares many characteristics with other coronaviruses, altered signaling pathways may contribute to the discovery of new COVID-19 therapeutics [3]. From this point of view, cellular interaction by angiotensin-converting enzyme 2 (ACE2) [4–9] and cytokine storm [10–12] can be considered interesting. Furthermore, it has been demonstrated that SARS-CoV-2 trafficking can be facilitated by Golgi fragmentation *via* downregulation of Golgi-reassembly-stacking protein of 55 kDa (GRASP55) [13]. In addition, the Raf/MEK/ERK signaling pathway has been shown to have a significant impact on viral pathogenesis, suggesting that stimulation of the Raf/MEK/ERK pathway by SARS-CoV-2 can contribute to viral survival, and therefore inhibitors targeting the mentioned signaling axis could be promising antiviral drug targets for COVID-19 [14].

The role of SARS-CoV-2 signaling in cell proliferation and death has caught the interest in establishing a network on virus-host protein-protein interactions by isolation of 26 SARS-CoV-2 proteins [15]. It was discovered that 332 human proteins were targeted by SARS-CoV-2, of which 69 FDA-approved drugs could be repurposed for COVID-19 treatment. Out of 46 proteins being known to be associated with cancer or cancer candidates, 23 have been or are currently under clinical evaluation in cancer patients [16]. As cancer cells and pathogens employ similar molecular pathways for the control of apoptosis and evasion of host defense, infection with both RNA and DNA viruses has been associated with the activation of cellular oncogenes or decrease in tumor suppression leading to oncogenesis. This approach demonstrates that system-wide integration of protein–protein interactions that drive viral pathogenicity and cancer has the potential to identify important factors responsible for the dysregulation of cellular mechanisms and development of novel drugs [15]. In this review we present the importance of the COVID-19 signalosome pathways, which could open novel alternative approaches for therapeutic interventions against SARS-CoV-2.

2. Signaling and potential therapeutic implementations of SARS-CoV-2 key targets

In therapeutic and prophylactic attempts against SARS-CoV-2, especially related to vaccine development, the S protein has been a commonly used target. As the S protein binds to the ACE2 on host cells initiating viral cell entry, it represents an obvious target for both drug and vaccine development [17]. However, proteases and other SARS-CoV-2 structural proteins play important roles in signaling and have therefore received significant attention.

2.1. Proteases

Proteins associated with SARS-CoV-2 include proteases such as RNA-dependent RNA polymerase (RdRp), 3-Chymotrypsin-like Protease (3CLPro), Papain-like protease (PLpro) and Helicase (nsP13) Lpro [18], which have been considered as targets for antiviral drug development against SARS-CoV-2 (Table 1).

2.1.1. RNA-dependent RNA polymerase (RdRp)

RdRp is a potential target as it is most conserved across several viral species including influenza virus, hepatitis virus C (HCV), Zika virus (ZIKV) and coronaviruses. In addition, RdRp plays an important role in viral RNA replication [19]. In the case of coronaviruses, RdRp catalyzes RNA genome synthesis by generation of a complementary minus strand RNA from the plus strand RNA template, which is initiated either by *de novo* (primer-independent) or primer-dependent RNA synthesis [20,21]. A number of RdRp inhibitors have been developed and previously evaluated as antivirals for other viruses. Due to the COVID-19 pandemic, they have now been repurposed for targeting SARS-CoV-2. In a molecular docking study, the RdRp of SARS-CoV-2 was modelled and targeted using different anti-polymerase drugs currently approved against other viruses [22]. The modelling suggested that remdesivir (RDV), ribavirin (RBV), sofosbuvir, galidesivir and tenofovir could be potent drugs against SARS-CoV-2 as they show high binding affinity to RdRp. Moreover, the guanosine derivative IDX-84, setrobuvir and YAK are potential candidates for SARS-CoV-2 therapy.

Previously, RDV has demonstrated therapeutic efficacy against Ebola virus (EBOV) in rhesus monkeys [23]. Moreover, RDV has shown favorable antiviral activity against different coronaviruses such as HCoV-229E, HCoV-OC43, SARS-CoV and MERS-CoV *in vitro* in human cell lines and primary cells [19]. Evaluation in a mouse model demonstrated that RDV reduced viral SARS-CoV loads and reduced pathological symptoms [24]. Similar results were obtained in MERS-CoV infected rhesus macaques [25]. In the case of SARS-CoV-2, RDV potently blocked virus infection in Vero E6 cells and based on RT-PCR and Western blotting analyses virus yields were significantly reduced [26].

Moreover, RDV reduced lung inflammation and virus titers in rhesus monkeys infected with SARS-CoV-2 [27]. In a placebo-controlled clinical study, the time to recovery of hospitalized COVID-19 patients was beneficial and the impact on mortality was positive [28]. In another study, COVID-19 patients receiving RDV had a median recovery time of 10 days compared to 15 days for the placebo group [29]. The mortality rate for patients treated with RDV was 6.7% compared to 11.9% for the placebo group by day 15, and 11.4% for RDV and 15.2% for placebo at day 29. The percentage of serious adverse events was also lower for RDV (24.6%) than placebo (31.6%). Moreover, patients treated with RDV had fewer respiratory tract infections. In October 2020 RDV was approved by the FDA for COVID-19 treatment in hospitalized adult and pediatric patients [30].

Favipiravir (FPV), a guanine analogue which selectively inhibits viral RdRp with a broad antiviral activity has been applied against influenza A, B and C viruses, EBOV, and Lassa virus (LASV) [31,32]. FPV has also shown synergistic effect in combination with the influenza virus neuraminidase (NA) inhibitor oseltamivir in mice [32]. FPV and interferon-α (IFN-α) treatment was compared to control treatment with lopinavir/ritonavir (LPV/RTV) in a phase I clinical trial [33]. The study showed that there were fewer adverse events for FPV treatment, the viral clearance time was shorter for patients treated with FPV (4 days) compared to the control group (11 days), and significant improvement in chest computed tomography (CT) was observed after FPV treatment (91.43%) compared to 62.2% in LPV/RPV treated patients. In another clinical trial in China, FPV showed significantly higher recovery rates and shortened latency to relief for pyrexia and cough compared to umifenovir [34]. Moreover, a retrospective observational study in Thailand showed clinical improvement in COVID-19 patients by day 7 [35] and a prospective, randomized, open-label trial comparing early and late FPV treatment in hospitalized COVID-19 patients in Japan suggested a trend toward better viral clearance on day 6 for the early treatment group (66.7%) compared to the late group (56.1%) [36].

Table 1
Proteases as targets for SARS-CoV-2 for the treatment of COVID-19.

Target/Drug	Findings	References
RdRp		
RDV	Blocking of viral infection in Vero cells	[26]
	Reduced lung inflammation and viral titers in monkeys	[27]
	Shortened recovery time, reduced mortality rates for COVID-19	[28,29]
	Approved for COVID-19 treatment in October 2020	[30]
FPV	Shortened treatment, improved chest CT compared to LPV/RPV	[31]
	Significantly higher recovery rates in patients	[34]
	Clinical improvement in patients	[35]
	Improved viral clearance	[36]
	Approval in Russia, Bangladesh, Pakistan, Jordan, Egyp	[36]
RBV	Anti-SARS-CoV-2 activity in Vero cells	[37]
	Shortened time from treatment start to negative PCR test	[38]
	No improvement in negative conversion time or mortality	[39]
Sofosbuvir	Shortened recovery, lower mortality in patients	[41,42]
	No difference in hospitalization or number of deaths	[43]
Galidesivir	No clinical benefit, clinical trial discontinued	[44]
EIDD-2810 (Molnupiravir)	Significantly reduced viral load in ferrets	[45]
	Inhibition of SARS-CoV-2 in mice	[46]
	Clinical trials on safety, tolerability and efficacy in progress	[47,48]
	Reduced hospitalization risk in two phase I trials	[49]
	Approved in the UK and by the FDA in the US	[50]
3CLPro		
Boceprevir	Inhibition of SARS-CoV, MERS-CoV and SARS-COV-2 in cell	[51]
	Reduced SARS-CoV-2 RNA in Vero cells	[51]
Ivermectin	Reduced SARS-CoV-2 transmission in non-severe COVID-19	[52]
	No difference in PCR positivity compared to placebo	[53]
	Meta-analysis showed no reduction in recovery time, mortality	[54]
	No clinical benefits compared to placebo in clinical trial	[55]
Paxlovid	89% reduced risk of hospitalization/death; FDA approval	[56]
PLPro		
Nathalene	Inhibition of SARS-CoV-2 replication in Vero cells	[57]
GRL-0617	Reduced viral infection in CaCo-2 cells	[58]
Helicase LPro I		
Quercetin	IC50 of 8.1 μM against SARS-CoV helicase	[59]
7-O-AMQ derivatives	IC50 of 2.7–5.2 μM against SARS-CoV helicase	[60]
Myricetin	IC50 of 2.71 μM against SARS-CoV helicase	[61]

3CLpro, 3-chymotrypsin-like protease; 7-O-AMQ der, 7-*O*-arylmethylquercetin derivatives; FPV, favipiravir; LPV, lopanivir; PLpro. Papain-like protease; RdRp, RNA dependent RNA polymerase; RDV, remdesivir; RPV, ritonavir.

Despite observation of clinical benefits for mild and moderate COVID-19 cases and need of large randomized controlled trials, FPV has been commercialized in countries such as Russia, Bangladesh, Pakistan, Jordan, Egypt, and Saudi Arabia [36].

Another guanosine analogue, ribavirin (RBV) has also been evaluated for COVID-19 treatment. Anti-SARS-CoV-2 activity of RBV was demonstrated in Vero E6 cells infected with SARS-CoV-2 [37]. Furthermore, *in silico* analysis indicated a broad-spectrum impact of RBV on Vero E6 cells. RBV also decreased transmembrane protease serine 2 (TMPRSS2) expression at both mRNA and protein levels and can potentially provide antiviral activity against SARS-CoV-2. In an open-label randomized, phase II trial the triple combination of IFN-β-1b, LPV/RTV, and RBV was compared to LPV/RTV in hospitalized COVID-19 patients [38]. The combination therapy resulted in a significantly shorter time (7 days) from start of treatment to negative nasopharyngeal swab than for the control group (12 days). However, in another study, intravenous RBV administration was compared to supportive therapy in patients with severe COVID-19, which indicated that RBV therapy was neither associated with improved negative conversion time for SARS-CoV-2 nor an improved mortality rate [39].

Sofosbuvir, a potent RdRp inhibitor, has been subjected to several clinical trials in COVID-19 patients [40]. In a phase I trial, 35 COVID-19 patients received sofosbuvir and daclatasvir and 27 individuals were given RBV [41]. The encouraging results demonstrated a median duration hospitalization of only 5 days for the sofosbuvir/daclatasvir group compared to 9 days for the RBV group. The mortality was also much lower (6%) for sofosbuvir/daclatasvir treatment compared to 33% after treatment with RBV. In another clinical trial, sofosbuvir/daclatasvir treatment was compared to standard of care alone [42]. The clinical recovery in the sofosbuvir/daclatasvir arm was better (88%) compared to 67% in the control arm. The median duration of hospitalization was also significantly shorter in patients receiving sofosbuvir/daclatasvir (6 days) compared to the control patients (8 days). In a single center, randomized, controlled phase I trial, sofosbuvir/daclatasvir combined with RBV was compared to standard of care [43]. There was no difference in median duration (6 days) of hospital stay between the groups, the number of intensive care unit (ICU) admissions was not significantly lower for patients receiving sofosbuvir/daclatasvir, and there was no difference in the number of deaths between the two groups. Although there were trends suggesting better recovery and lower death rates in patients treated with sofosbuvir/daclatasvir, the randomized trial was too small to make definitive conclusions.

Galidesivir, an adenosine nucleoside analogue that blocks viral RNA polymerase, has also been presented as a target for anti-SARS-CoV-2 therapy [62]. Although some promising findings were obtained in pre-clinical studies, early-stage clinical trial results showed no benefit of galidesivir compared to placebo and the study was discontinued [44]. Another COVID-19 drug candidate, the ribonucleotide analogue EIDD-2801, showed a significant reduction in SARS-CoV-2 viral load in the upper respiratory tract and completely suppressed spread to untreated contact animals in a ferret model [45]. Moreover, EIDD-2801 inhibited SARS-CoV-2 in human epithelial cells in culture and several coronaviruses in mice [46]. The first-in-human phase I trial has been conducted in healthy volunteers to assess the safety, tolerability and pharmacokinetics of EIDD-2801 [47]. Molnupiravir (EIDD-2801) has also been subjected to a multi-center, randomized, double-blind, placebo-controlled phase II clinical trial for the evaluation and safety in hospitalized COVID-19 patients [48]. Moreover, a significant reduction in both hospitalization and death rates in patients with mild COVID-19 was seen in two phase I clinical trials [49]. Initially, molnupiravir was approved in the UK, but the efficacy of only 30% reduced risk of hospitalization delayed granting EUA by the FDA [50].

2.1.2. 3-chymotrypsin-like protease (3CLPro)

The 3CLpro also called Mpro is the main protease pivotal for the replication of SARS-CoV-2 [63]. A number of inhibitors against 3CLPro were identified by computational molecular modelling of 3987 FDA approved drugs, of which 47 were selected for inhibition studies of SARS-CoV-2 specific 3CLPro *in vitro*. For instance, boceprevir, ombitasvir, paritaprevir, tipranavir, ivermectin and micafungin showed inhibition against 3CLPro. Boceprevir as well as calpain inhibitors inhibited SARS-CoV, MERS-CoV and SARS-CoV-2 in cell culture and further showed a synergistic effect with RDV [51].

Ivermectin, an FDA-approved parasitic broad spectrum anti-parasitic agent [64], has demonstrated anti-viral activity against a wide range of viruses [65]. Moreover, ivermectin has been shown to limit infections of RNA viruses, but has also been effective against DNA viruses [65]. In Vero cells infected with SARS-CoV-2 ivermectin caused a 93% reduction in viral RNA in the medium (released viral particles) and 99.8% reduction in cell-associated viral RNA at 24 h. At 48 h an approximately 5000-fold reduction in viral RNA was observed [52]. Ivermectin has also been subjected to a pilot, double-blind, placebo-controlled, randomized clinical trial for the evaluation of the efficacy of a single dose for the reduction of transmission of SARS-CoV-2 in patients with non-severe COVID-19 [53]. The viral load and infectivity were determined by detection of SARS-CoV-2 RNA by PCR from nasopharyngeal swabs 7 days post-treatment. The results indicated that there was no difference in the proportion of PCR positives in the ivermectin and placebo groups. Although a marked reduction of self-reported anosmia/hyposmia, a reduction of cough and a tendency of lower viral loads and lower SARS. CoV-2 IgG titers were reported, additional larger clinical trials are needed to demonstrate efficacy of ivermectin. Furthermore, a meta-analysis on ivermectin treatment of ambulatory and hospitalized COVID-19 patients on randomized controlled trials and retrospective cohorts was carried out [54]. Twelve studies including 5 retrospective cohort studies, 6 randomized clinical trials, and 1 case series, showed no reduction in mortality or reduced patient recovery time after ivermectin treatment. Moreover, all studies presented a high risk of bias and a very low certainty of evidence. For this reason, there is insufficient certainty and quality of evidence to support the recommendation of using ivermectin for COVID-19 prevention and treatment. The FDA stated that ivermectin has not been approved for prevention or treatment of COVID-19 www.fda.gov/animal-veterinary/product-safety-information/faq-covid-19-and-ivermectin-intended-animals). In a recent clinical trial in Brazil, patients with COVID-19 were treated with ivermectin and compared to placebo [55]. The study demonstrated no significant effects of ivermectin on secondary outcomes or adverse events. There was no reduction incidence of hospital admission due to progression of COVID-19 or prolonged emergency department observation among outpatients. In contrast, interim results from a phase II/III study on the 3CLpro inhibitor Paxlovid in 1219 adults showed that the risk of COVID-19 related hospitalization and death from any cause was 89% lower than for those individuals who received placebo [56]. The FDA granted EUA for Paxlovid in December 2021.

2.1.3. Papain-like protease (PLpro)

In search of drug targets, the PLpro domain as part of the non-structural protein 3 (nsp3) of SARS-CoV-2 has been considered for evaluation of PLpro inhibitors due to their vital involvement in viral replication [66]. In this context, data mining of the conformational database of FDA-approved drugs identified 147 potential SARS-CoV-2 inhibitors [67]. For instance, PLpro inhibitors such as ubiquitin (Ub), interferon-stimulated gene product 15 (ISG15) and naphthalene were evaluated for SARS-CoV-2 inhibition [57]. However, Ub showed a less marked reduction compared to SARS-CoV, and ISG15 was more prominent against MERS-CoV inhibition. In contrast, naphthalene demonstrated both inhibition of SARS-CoV-2 PLpro activity and SARS-CoV-2 replication in Vero E6 cells [57]. In another approach, the PLpro inhibitor GRL-0617 showed impaired cytopathogenic effect, maintained the antiviral interferon pathway, and reduced viral replication in infected CaCo-2 cells [58].

2.1.4. Helicase (nsP13) Lpro

In the case of SARS-CoV-2, the helicase encoded by nsP13 is critical for viral replication and therefore poses a potential alternative target for anti-COVID-19 therapy [68]. Application of homology modelling and molecular dynamics made it possible to generate structural models of the SARS-CoV-2 helicase and perform a virtual screening of 970.000 chemical compounds. Lumacaftor and cepharanthine displayed significant inhibition of purified recombinant SARS-CoV-2 helicase with IC50 values of 0.3 and 0.4 nm, respectively. Lumacaftor can act as a chaperone for protein folding and cepharanthine has already previously been described as an inhibitor of SARS-CoV [69]. Bananins have proven efficient inhibitors of the ATPase activity of the SARS-CoV helicase in the IC50 range of 0.5–3 μM and due to the high homology between SARS-CoV and SARS-CoV-2 helicases (99.8%) [69], they could also be potential targets for COVID-19 therapeutics [70].

Interestingly, flavonoid phytomedicines such as caflanone, equivir, hesperitin, myricetin, and linebacker have been considered as potential prophylactics or therapeutics against SARS-CoV-2 [71]. Especially equivir has demonstrated inhibition of helicase activity contributing to the prevention or reduction of viral entry. Although *in silico* modelling and *in vitro* testing have proven promising, the poor bioavailability of flavonoids has hampered *in vivo* applications [72]. For this reason, flavonoids have been encapsulated in nanoparticles (nanodrones) or conjugated as targeting moieties on nanodrones [73]. Previously, quercetin [59], 7-*O*-arylmethylquercetin derivatives [60], and myricetin [61] have demonstrated IC50 affinities in the range of 2.7–8.1 μM against SARS-CoV helicase making them potential agents against SARS-CoV-2 due to the high homology of SARS-CoV and SARS-CoV-2 helicases.

2.2. Structural proteins

The SARS-CoV-2 structural proteins have been common therapeutic targets, especially for vaccine development (Table 2). The most commonly studied target is the S protein (S) [17]. However, other structural proteins such as the envelope (E), nucleocapsid (N), and membrane (M) proteins can also be attractive for development of prophylactics and therapeutics.

2.2.1. Spike protein (S)

The S protein plays a prominent role in SARS-CoV-2 infection by binding to the angiotensin converting enzyme 2 (ACE2) promoting viral entry into host cells [74]. The S protein contains the receptor binding domain (RBD), which is essential for binding to ACE2 [75]. For this reason, SARS-CoV-2 S has frequently been targeted for the development of antiviral drugs, monoclonal antibodies, and vaccines [76].

In the context of antiviral drug development, a number of small molecule compounds have demonstrated high binding affinity against the S protein [77]. Although this is the case for many anti-hypertensive, antifungal, antibacterial, anti-coagulant drugs and natural flavonoids, they are not predicted to cover the binding interface of the S-ACE2 complex. In contrast, hesperidin is predicted to occupy the middle shallow pit of the surface of the RBD of the S protein. Superimposing the ACE2-RBD complex to the hesperidin-RBD complex indicated that hesperidin may disrupt the interaction of ACE2 and RBD and interfere with viral entry. Due to this anti-viral activity, hesperidin, a classical herbal medicine used as an antioxidant and anti-inflammatory agent, might constitute a treatment option for COVID-19 through improving the host immune response against infection [78]. As hesperidin is present in citrus fruits such as oranges the role of nutrition should not be underestimated as a means of prevention of COVID-19 [79].

One therapeutic approach comprises of developing monoclonal antibodies (mAbs) against SARS-CoV-2. In this context, the potential of mAbs for therapeutic interventions has been addressed. The cross-reactivity of the mAb CR3022 against SARS-CoV was analyzed related to its cross-reactivity to SARS-CoV-2 [80]. Although the epitope of CR3022 did not overlap with the SARS-CoV-2 RBD, potent binding of KD 6.3 nM was obtained, indicating that CR3022 could be developed alone or in combination with other neutralizing antibodies for the prevention and treatment of COVID-19. In contrast, some of the most potent SARS-CoV-specific neutralizing antibodies targeting the ACE2 binding site of SARS-CoV did not show binding affinity to the SARS-CoV-2 S. It is therefore necessary to developed novel mAbs, which specifically bind to the SARS-CoV-2 S RBD. For this reason, a human mAb was identified

Table 2
Structural proteins as targets for SARS-CoV-2 for the treatment of COVID-19.

Target/Drug	Findings	Ref
Spike		
Drugs & mAbs		
Hesperidin	High binding affinity against SARS-CoV-2 S	[78]
CR3022 mAb	Binding affinity for both SARS-CoV/SARS-CoV-2 S	[80]
47D11 mAb	Neutralization of SARS-CoV/SARS-CoV-2 in Vero cells	[81]
S309	Targeting of highly conservative S epitope	[82]
VIR-7381 (Sotrovimab)	Improved half-life of S309, phase II/III trial in progress	[83]
LY-CoV55 (Bamlavinimab)	High binding affinity to SARS-CoV-2 S RBD	[84]
	Good safety and tolerability in phase I	[85]
	Lower severity of COVID-19 compared to placebo in phase II	[86]
LY-CoV016 (Etesimivab)	No significant improvement, phase III discontinued	[89]
LY-CoV555 + LY-CoV106	EUA by the FDA for mild-to-moderate COVID-19	[90]
REGN10987 + REGN10933	Targeting of SARS-CoV-2 S epitopes	[91]
	Decreased lung titers in hamsters, reduced viral load in macaques	[92]
	Good safety profile, reduced viral load in phase II/III	[93]
—	Prevention of SARS-CoV-2 and COVID-19 in phase III	[94]
	FDA authorization for use in adult and pediatric COVID-19 patients	[95]
Vaccines		
NVX-CoV2373(Rec-S)	Protection against SARS-CoV-2 in macaques	[98]
	>90% vaccine efficacy in Phase III	[99]
	Conditional marketing authorization granted in the EU and the UK	[100]
Ad5-S nb2	Protection against SARS-CoV-2 in macaques	[101]
	>90% vaccine efficacy in clinical trials	[102]
	Emergency use authorization in China	[103]
ChAdOx1 nCoV-19	Protection against SARS-CoV-2 in macaques	[104]
	62.1–90% vaccine efficacy in clinical trials	[105]
	Emergency use authorization in the UK	[106]
rAd26-S/rAd5-S	Good safety, robust immunogenicity in animal models	[107]
	Good safety and tolerability in Phase I/II	[108]
	91.6% vaccine efficacy in Phase III	[109]
	Emergency use authorization in Russia in July 2020	[110]
Ad26.CoV2.S	Protection against SARS-CoV-2 in macaques	[111]
	Strong immunogenicity of clinical trials	[112]
	Emergency use authorization by the FDA	[113]
DNA-S	Protection against SARS-CoV-2 in macaques	[114]
DNA INO-4800	Safety and tolerability, robust immunogenicity in phase I/II	[115]
	Durable immune responses in phase I	[116]
LNP mRNA-1273	Protection against SARS-CoV-2 in mice	[117]
	Protection against SARS-CoV-2 in primates	[118]
	Phase I: SARS-CoV-2 specific robust immune responses	[119,120]
	Phase III: 94.1% vaccine efficacy	[121]
	Vaccine approval in the USA, UK, and Europe	[122]
LNP RNA BNT162b1/ BNT162b2	Protection against SARS-CoV-2 in macaques	[123]
LNP RNA BNT162b2	Phase I/II: Good safety and immunogenicity	[124,125]
	Phase III: 95% vaccine efficacy	[126]
	Vaccine approval in the USA, UK and Europe	[127]
Envelope		
Amantadine	Potential target for SARS-CoV-2 inhibition	[128]
Gliclazide	Potential targets for COVID-19 therapy	[129]
Memantine	Potential targets for COVID-19 therapy	[129]
Nucleocapsid		
N epitopes	Screening of B and T cell epitopes for vaccines	[130]
PJ34	Inhibition of HCoV OC43 replication	[131]
P3	Antiviral activity against MERS-CoV	[132]
Membrane		
M epitopes	Targets for vaccines and T cell therapy	[133]

Ad, adenovirus; Ch-VSV, chimeric vesicular stomatitis virus with SARS-CoV-2 spike protein; LNP, lipid nanoparticle; mAb, monoclonal antibody; MVA, modified vaccinia virus Ankara; NDV, Newcastle disease virus; P3, 5-benzyloxygramine inhibitor; PJ34, N protein inhibitor.

from a collection of 51 SARS-CoV-2 S hybridomas from immunized transgenic H2L2 mice [81]. The human mAb 47D11 exhibited neutralizing antibodies against both SARS-CoV and SARS-CoV-2 S proteins. The 47D11 mAb demonstrated potent inhibition of Vero E6 cell growth infected with SARS-CoV-2 and SARS-CoV S pseudotyped vesicular stomatitis virus (VSV). Moreover, neutralization by 47D11 was also achieved in Vero E6 cells infected with SARS-CoV-2 and SARS-CoV. It was also shown that 47D11 targeted the RBD of SARS-CoV-2 and SARS-CoV. Furthermore, the S309 mAb, isolated from a convalescent SARS patient in 2003, targeted a highly conservative S protein epitope and therefore also neutralized SARS-CoV-2 [82]. To extend the half-life of S309, the VIR-7831 mAb (sotrovimab) was engineered and is currently evaluated in a phase II/III trial [83]. Moreover, LY-CoV555 (bamlanimiab), a fully humanized neutralizing IgG1 mAb, targets the SARS-CoV-2 S RBD, showing the highest binding affinity among 500 evaluated antibodies [84]. The safety, tolerability and pharmacokinetics of intravenous LY-CoV555 has been under evaluation in hospitalized COVID-19 patients in a phase I trial [85]. Interim results from a phase II trial showed a slightly lower severity of symptoms in COVID-19 patients treated with LY-CoV555 compared to placebo and appeared to accelerate the natural decline in viral load [86]. Moreover, another mAb, LY-CoV016 (etesemivab), targeting another S protein epitope has been engineered [87]. In a phase II/III study, LY-CoV555 was applied to 577 non-hospitalized COVID-19 patients as monotherapy or in combination with LY-CoV016 [88]. No difference in viral load could be detected after treatment with LY-CoV555 or placebo. However, the combination of LY-CoV555 and LY-CoV016 showed a statistically significant reduction in viral load. Additionally, although LY-CoV555 showed comparable safety to RDV, a phase III trial was discontinued because no improvements were detected in hospitalized COVID-19 patients [89]. However, positive findings from studies on LY-CoV555 led to the EUA) by the FDA for treatment of mild-to-moderate COVID-19 in adult and pediatric patients [90]. The mAbs REGN10987 (imdevimab) and REGN10933 (casirivimab) have been engineered to target different epitopes of the SARS-CoV-2 S RBD [91]. Preclinical studies with the REGN-COV2 mAb cocktail (REGN10987 + REGN10933) showed greatly decreased lung titers in golden hamsters and reduced viral loads in rhesus macaques [92]. Interim results for a phase II/III trial generated a good safety profile and reduced viral load in COVID-19 patients [93]. In a phase III study, it was demonstrated that the REGN-COV2 mAb cocktail prevented symptomatic COVID-19 and asymptomatic SARS-CoV-2 infections in households where previously uninfected individuals came into contact with SARS-CoV-2 infected persons [94]. In October 2021, REGN-COV2 was authorized for the treatment of mild-to-moderate COVID-19 in adult and pediatric (age 12 and older) patients, who are at high risk for progression of severe COVID-19 [95].

The majority of prophylactic and therapeutics initiatives related to the S protein involves vaccine development although inactivated viral particles have also been used. The large number of preclinical and clinical studies have been reviewed in detail elsewhere [96,97], and therefore, only a summary is presented here and in Table 2. Both the full-length S protein and specific regions such as the RBD have been applied as antigens for induction of immune responses. Vaccine candidates have been generated by recombinant protein expression, delivery of viral vectors, virus-like particles, or nucleic acids. All above mentioned approaches have elicited robust immune responses in immunized animals and in many cases provided protection against SARS-CoV-2 challenges in rodents and primates (Table 2). Several vaccine candidates have also received EUA.

In this context, the vaccine candidate NVX-CoV2373, a nanoparticle-encapsulated full-length SARS-CoV-2 S protein expressed in insect cells, protected the upper and lower airways of immunized cynomolgus macaques from SARS-CoV-2 challenges [98]. The NVX-CoV2373 vaccine candidate was evaluated in a phase III study, where over 90% efficacy was observed with most breakthrough cases caused by contemporary variant strains [99]. Both the EU and Great Britain have granted Conditional Marketing Authorization (CMA) for NVX-CoV2373 [100].

Adenovirus vectors have been frequently used for COVID-19 vaccine development. For example, the human adenovirus serotype 5 (Ad5) (Ad5-S nb2) [101] and the chimpanzee adenovirus ChAdOx1 [104] expressing the full-length SARS-CoV-2 S protein provided protection against challenges with SARS-CoV-2 in macaques after two immunizations. In an approach to reduce any immune response against the adenovirus vector itself leading to compromised vaccine efficacy, a prime-boost strategy of prime vaccination with Ad26-SARS-CoV-2 S followed by Ad5-SARS-CoV-2 vaccination showed efficacy in preclinical animal models [107]. Moreover, the Ad26.COV2·S vaccine based on the Ad26 serotype is unique in that sense that only a single immunization is required for induction of neutralizing antibodies and protection in macaques [111]. In the context of clinical trials, the Ad5-S nb2 vaccine demonstrated over 90% efficacy [102] and has received EUA in China [103]. Several clinical trials for ChAdOx1 nCoV-19 demonstrated safe delivery and high vaccine efficacy [105] and EUA was granted in the United Kingdom in December 2020 [106]. Moreover, the Ad26.COV2·S vaccine candidate has also shown strong immunogenicity in clinical trials [112] and has received EUA from the FDA in February 2021 [113]. The rAd26-S/rAd5-S (Sputnik) vaccine showed also good tolerability and 91.6% efficacy in phase I/II [108] and phase III [109] trials. Controversially, the Sputnik vaccine was granted EUA in Russia before any results from preclinical studies had been published and the vaccine had been tested in only 76 volunteers [110]. Other viral vectors such as lentiviruses, vaccinia viruses, Newcastle disease virus (NDV), measles viruses, VSV, Venezuelan equine encephalitis virus (VEE), and influenza virus have also been applied for COVID-19 vaccines as previously reviewed [134].

In the case of nucleic acid-based vaccines, plasmid DNA expressing the full-length SARS-CoV-2 S gene demonstrated protection against SARS-CoV-2 challenges in immunized macaques [114]. In the case of clinical trials, intradermal administration combined with electroporation of plasmid DNA carrying the full-length S protein (INO-4800) showed excellent safety and tolerability and either humoral or cellular immune responses in a phase I [115]. Furthermore, durable antibody responses were detected in another phase I study on INO-4800 [116].

In the case of mRNA-based vaccines, lipid nanoparticle (LNP)-encapsulated mRNA vaccine candidates have proven efficient in eliciting immune responses and providing protection in mice [117] and primates [118] based on expression of the prefusion-stabilized full-length SARS-CoV-2 S. Additionally, the LNP-mRNA vaccine candidates BNT162b1 and BNT162b2, containing the SARS-CoV-2 S RBD and full-length SARS-CoV-2 S protein sequences, respectively, provided protection in immunized macaques [123]. In the context of clinical evaluations, the LNP-encapsulated mRNA-1273 induced SARS-CoV-2-specific immune responses in all participants in a phase I trial [119]. Moreover, another phase I study demonstrated higher neutralizing antibody titers with a dose of 100 μg RNA compared to 25 μg [120]. In a phase III study, the mRNA-1273 vaccine candidate showed, aside from transient local and systemic reactions, no serious adverse events and provided 94.1% efficacy preventing serious COVID-19 manifestation [121]. The mRNA-1273 vaccine received EUA in the USA in December 2020 and later in a number of countries [122]. Good safety and immune responses in phase I/II clinical trials have also been demonstrated for both the LNP-mRNA S RBD (BNT162b1) [124] and LNP-mRNA full-length S [BNT162b2) [125]. Furthermore, a two-dose administration of BNT162b provided 95% protection against COVID-19 in adults in a phase III study [126]. The BNT162b vaccine was the first COVID-19 vaccine to be approved in several countries [127].

2.2.2. Envelope (E)

The coronavirus envelope (E) protein is assembled into cation-selective ion channels, which are involved in virus budding and release and host inflammation responses [135]. Heaxamethylene amiloride (HMA) [136] and amantadine [137] block the channel activity of the E protein and present potential antiviral and vaccine targets. In the case of amantadine, antiviral therapeutic effects have been demonstrated against influenza virus [137] and lack of E protein has been shown to attenuate *in vivo* damage in SARS-CoV infected mice [128]. Furthermore, screening of SARS-CoV-2 E channel inhibitors identified Gliclazide and Memantine as potential targets for COVID-19 antiviral drugs [129].

2.2.3. Nucleocapsid (N)

Related to the SARS-CoV-2 nucleocapsid (N) protein, it was demonstrated that a number of epitopes could be identified as potential vaccine targets by screening of SARS-CoV-derived B and T cell epitopes [130]. It was found that the identified set of SARS-CoV epitopes mapped identically to SARS-CoV-2 and thereby present potentially interesting targets for vaccine development against COVID-19. In another approach, it was demonstrated that in addition to ORF6 and ORF8, the SARS-CoV-2 N protein strongly inhibited the type 1 interferon signaling pathway, which could reveal novel targets for drug and vaccine development [138]. Furthermore, structure determination of the N protein has provided insight into novel drug targets against SARS-CoV-2 [139]. Blocking of the RNA binding activity of the N protein affects viral RNP formation and genome replication. For instance, the compound PJ34 has previously been shown to target the ribonucleotide binding site at the N-terminal domain of the N protein (N-NTD) of the HCoV-OC43, leading to inhibition of viral replication [131]. Comparison of the corresponding binding site for PJ34 in the SARS-CoV-2 N-NTD structure indicated that the key residues were conserved [139]. Alternatively, the normal N protein oligomerization can be blocked, leading to termination of RNP formation or abnormal aggregation. In this context, the 5-benzyloxygramine (P3) inhibitor was shown to mediate MERS-CoV N-NTD non-native dimerization and induction of N protein aggregation, resulting in potent antiviral activity against MERS-CoV [132]. It was discovered that almost all residues in the binding cavity of P3 in the SARS-CoV-2 N-NTD were conserved in comparison to MERS-CoV, making this approach attractive for drug development against COVID-19.

2.2.4. Membrane protein (M)

The SARS-CoV-2 membrane (M) protein is composed of three transmembrane domains forming the structural blocks of viral particles that support viral assembly [140]. The M protein functions together with the E, N and S proteins in the process of RNA packaging [141]. Moreover, the M protein plays a role in intracellular homeostasis and elicits neutralizing antibodies. In this context, SARS-CoV-2 specific T cells expanded from convalescent COVID-19 donors recognized immunodominant viral epitopes in conserved regions of the SARS-CoV-2 S, N and M proteins [133]. This allowed the identification of several highly

conserved epitopes of the M protein, which could be attractive targets for vaccine and T-cell therapy. This approach should support the prevention of early treatment of SARS-CoV-2 infections in immunocompromised patients.

3. SARS-CoV-2 infected host signaling pathways targets and potential therapeutic implementations

Surface proteins of invading microbes are the first ones to be recognized by the immune system. Moreover, systemic and specific immune actions are activated against pathogens. For some diseases, however, microbes can evade the immune system leading to pathological conditions. Thus, strengthening the immune response through synthetic drugs might help to restore the body's defense system and fight against the infection. Therapeutic targets have been searched for to combat SARS-CoV-2 infections. As mentioned previously,the SARS-CoV-2 proteases and structural proteins have been evaluated as potential targets for drug and vaccine development. However, it is essential to increase the scope to other proteins, which are involved in the regulation of SARS-CoV-2 infection. These targets and drug development efforts are described below and summarized in Table 3.

3.1. Renin-angiotensin system (RAS)

The RAS pathway is one of the essential biochemical pathways of various neurovascular disorders. It has become apparent that the mechanism of RAS facilitates other functions besides blood pressure (BP) regulation. The RAS plays a vital role in pathophysiological impairment, including stroke and retinopathy in various neurovascular disorders. Angiotensin II (Ang II) is a polypeptide hormone cleaved by the Angiotensin converting enzyme (ACE). Angiotensin I (Ang I) itself is generated by angiotensinogen cleavage of the renin enzyme. Even though the renin precursor, prorenin, previously presumed to be inactive, its cleavage was also shown to be catalyzed when coupled to its receptor, (pro)renin receptor [142]. Ang II induces two distinct brain receptors, type 1 Ang II (AT1R) receptor and type 2 receptor (AT2R). AT1R is prevalent in adults showing its inflammatory and vasoconstrictor impact. Additionally, AT1R is divided into two subtypes AT1a and AT1b in rodents. AT2R is highly expressed during growth and in lower quantities in adulthood and may cause adverse effects, promoting vasodilation and reduced infection.

The Kallikrein Kinin System may present another potential association between RAS and vascular injury. It is well understood that bradykinin breaks down into desArg9-bradykinin, involved in endothelial dysfunction by activating the B1 receptor [143]. RAS is positioned at the center of COVID-19 pathogenesis with the discovery of ACE2 as the host cell receptor for SARS-CoV-2. In addition, since protease is involved in the angiotensin peptide metabolism affecting the regulation of the immune system, future RAS constituents might play a role in the pathogenesis of COVID-19. RAS is a regulatory proteolytic cascade with diverse physiological roles in various organs, like the heart, kidneys, and lungs [144]. RAS dysregulation is a well-established process for the development of many comorbidities, like hypertension and diabetes, known to increase the susceptibility to COVID-19 [145]. The first-line therapeutic strategy for both reduced cytokine generation and prevention of organ damage is the development of AT1R blockers (ARBs) and ACE inhibitors (ACEi). These promising effects have also been identified for recombinant ACE2 and Ang (1–7). Thus, there is a clinical potential to use ARB and ACEi combined with viral-targeted treatment to improve patient responses to SARS-CoV-2 infections [146]. However, it has been reported that there is an association between patients with severe COVID-19 and chronic use of ARB and ACEi. The upregulation of the expression of ACE2 caused by ARB and ACEi treatment may be one potential mechanism, as previously discussed, although expression of ACE2 in the lungs has not yet been studied in this scenario. This tentative theory led to the discussion of whether treatment with ARB and

Table 3
Therapeutic targets from signaling pathways.

Target/Drug	Findings	Ref
RAS		
ACE2		
APN01	Decrease in IL-6 plasma levels	[152]
TMPRSS2		
Camostat mesylate	TMPRSS2 inhibition	[153]
	Reduced viral infectivity in COVID-19 patients	[153]
Bromhexine hydrochloride	Prevention of viral entry	[153]
ER & Golgi		
Cathepsin L		
Ddec-RVKR-CMK	Inhibition of MERS-CoV entry	[154]
EST	Inhibition of SARS-CoV entry	[155]
MDL-28170	Inhibition of SARS-CoV entry	[156]
Oxocarbazate	Inhibition of SARS-CoV entry	[157]
SSAA09E1	Inhibition of SARS-CoV entry	[158]
Immune pathways		
Tociluzimab	Attenuated inflammation, inhibition of IL-6 signaling	[159]
Sarilumab	Attenuated inflammation, inhibition of IL-6 signaling	[159]
Fedratinib, ruxolinitinib	JAK/STAT inhibitors, attenuated cytokine storm	[159]
Fingolimod, Infliximab, adalimumab	S1Pr1 agonist, diminished cytokine storm	[160], [160]
Serine protease inhibitors	Blocking of TNF-α, decreased inflammatory process Decreased expression of TNF-α and IL-6	[160]
Anakinra	Inhibition of cytokines	[159]
	Decreased mortality, reduced hospitalization in phase III	[161]
Quercetin	Suppression of inflammasomes	[159]
Flufenamic acid	Selective inhibition of NLPR3 inflammasome	[161]
Hypoxia		
Heparin	No improved survival in critically ill COVID-19 patients	[162]
	Improved survival in noncritically ill COVID-19 patients	[163]
Melatonin	Reduced hypoxia, ferroptosis, hemoglobin denaturation	[164]
Calcium pathways		
Bepridil	Reduced infection by prevention of host cell entry	[172]
Amlodipine	Reduced infection by prevention of host cell entry	[172]
Nifedipine	Reduced infection by prevention of host cell entry	[172]
Vitamin D	Downregulated TLR2/TLR4, reduced inflammation	[172]
Other pathways		
Apilimod	Clinical evaluation in progress	[166]
Tetrandine (TPC2 inhibitor)	Potential inhibition of virus entry and replication	[167]
	Clinical evaluation in progress	[168]

Ddec-RVKR-CMK (ecanoyl-Arg-Val-Lys-Arg-chloromethylketone); ER, endoplasmic reticulum; EST [(23,25)trans-epoxysuccinyl-l-leucylamindo-3-methylbutane ethyl ester]; MDL-28170 (calpain inhibitor III, or *Z*-Val-Phe-CHO); RAS, renin-angiotensin system; SSAA09E1 {[(Z)-1-thiophen-2-ylethylideneamino] thiourea}; TLR, toll-like receptor; TPC, two-pore channel.

ACEi should be discontinued to reduce the susceptibility to COVID-19. However, there was immediate consensus that the ARB and ACEi treatment should be retained as there is insufficient evidence to support the removal of existing hypertension and diabetes treatment strategies [147]. The aim is to preserve controlled comorbidities and to prevent secondary incidents in COVID-19 patients. In a retrospective analysis, it was [148] confirmed that the mortality rate associated with COVID-19 in patients treated with ARB/ACEi was considerably lower than in untreated individuals [148]. Drugs such as the ACEi lisinopril, and the ARB losartan demonstrated increased expression of ACE2 mRNA in cardiac mice by lisinopril and losartan alone [149]. In combination, lisinopril and losartan increased the ACE2 activity, but not the expression of ACE2 mRNA.

3.1.1. ACE2

The comparison of SARS-CoV and SARS-CoV-2 is essential, as ACE2 is also the functional receptor for SARS-CoV. It was determined that ACE2 is expressed in 0.64% of all human lung cells and 83% of ACE2 expressing cells are type II alveolar (AT2) epithelial cells, indicating that these cells may act as a viral reservoir [150]. Furthermore, gene expression analysis demonstrated that multiple viral lifecycle-related genes were significantly overrepresented in ACE2-expressing AT2 cells, suggesting efficient SARS-CoV-2 replication capacity in the lungs. Therefore, several potential therapeutic approaches have been investigated to target ACE2. Structural biology approaches have identified interacting regions in the SARS-CoV/SARS-CoV-2 and ACE2 allowing engineering of antibodies and small molecules, which may block the SARS-CoV/SARS-CoV-2 from attaching to the ACE2 receptor. Moreover, overexpression of ACE2 in soluble form may competitively bind to and neutralize SARS-CoV-2 and rescue ACE2 cell activity, which negatively regulates the RAS for protection of lung damage [151]. Noticeably, recombinant human ACE2 (rhACE2; APN01, GSK2586881) was shown to be stable without adverse hemodynamical consequences in healthy participants and a small cohort of ARDS patients. APN01 administration quickly reduced the proteolytic target of angiotensin II peptides, resulting in decrease of plasma IL-6 levels [152].

3.1.2. TMPRSS2

The transmembrane serine 2 (TMPRSS2), also known as Epitheliasin, activates S2 protein proteolytic binding of SARS-CoV-2 to the ACE2 receptor for entry into host cells. *In vitro* experiments have shown that inhibition of TMPRSS2 does not entirely obstruct the entrance of viruses into host cells. Camostat mesylate is currently in clinical evaluation. It was demonstrated that camostat mesylate efficiently inhibited TMPRSS2, resulting in reduced viral infectivity in COVID-19 patients [153].

3.1.3. Furin

Although TMPRSS2 is the main enzyme that contributes to the entry of SARS-CoV-2 into host cells, this function is also present in several other serine proteases. Serine proteases, trypsin, elastase, and furin cleave the S protein in the SARS-CoV and MERS-CoV viral envelopes. Furin is a member of the network of trans-Golgi and is highly expressed in endothelial and pneumocyte cells. It was recently demonstrated to cleave SARS-CoV-2, as well [169]. Thus, viral cell entry relies on particular ACE2 binding and TMPRSS2 cleavage, but other serine proteases, such as plasmin, can replace the main proteases. Autopsies of COVID-19 patients have provided abundant fibrin deposition associated with increased action of plasmin activity. Plasmin can stimulate human macrophages to promote the development of pro-inflammatory cytokines such as IL-6, IL-8, IL-10, and TNF, in addition to its cleavage activity on viruses. An elevated IL-6 plasma level is a biomarker for "cytokine release syndrome" in COVID-19 patients with terrible outcomes [154]. The use of TMPRSS2 inhibitors, including Camostat mesylate and Bromhexine hydrochloride, has been recommended as potential therapeutics. They prevent viral penetration mediated by TMPRSS2 and operate as an inhibitor of TMPRSS2, respectively [153].

3.2. Endoplasmic reticulum and Golgi trafficking

Enveloped animal viruses have often been used to analyze protein transport and secretion, given that viral membrane proteins hijack the host cell protein transportation machinery, pursuing the same intracellular routes as endogenous host cell proteins. Therefore, membrane glycoproteins of most enveloped viruses migrate *via* the constitutive secretory route through the endoplasmic reticulum (ER) and Golgi apparatus onto the plasma membrane, where the assembly and budding of progeny virus occurs [170].

3.2.1. Cathepsin L (CatL)

Cathepsins represent a class of proteases that recycle cellular proteins inside the lysosomes. These proteases consist of serine, aspartate, and cysteine peptidases and are involved in endo- or exopeptidase activity. During translocation from the ER to the Golgi apparatus and the lysosomal and endosomal compartments, cathepsins are synthesized as inactive proenzymes or zymogens. Cathepsins require a reduced pH (between 4.5 and 5.0) for optimal activity, as found in the lysosome [171]. In different physiological processes, cathepsins play a significant role in cellular functions such as apoptosis, antigen treatment, remodeled extracellular matrix, and immune reactions of major histocompatibility complex (MHC) class II. Cysteine cathepsin is excessively secreted and is often associated with inflammation of different pathological conditions. In inflammatory cells, high levels of CatL can thus be activated under inflammatory conditions [172]. Viral S2 comprises the putative fusion peptide; the heptad repeats HR1 and HR2 and participates in the viral membrane fusion. The S1 subunits connect to the ACE2, and the S2 fuses during the entry of the virus, which allows viral genomes to reach the host cells. A cleavage by a host protease is required as a type I fusion protein to activate the fusion potential of the S protein. Host proteases such as proprotein convertases (furin), extracellular proteases (elastase), cell surface proteases (TMPRSS2) and lysosomal proteases (CatL and CatB) can be cleaved through several phases of the infection cycle. It has lately been reported that the endosomal CatL protease enzyme being utilized during cell entry rather than cell exit through the endosomal route. Several efforts to create CatL inhibitors have been advocated due to the biological importance of CatL. The first CatL cystatin inhibitor was isolated from *Aspergillus* in 1981, and additional molecules have been extracted since then. Inhibitors include epoxy succinic acid, beta-lactams, vinyl sulfone, and acyl hydrazine byproducts [173]. The most reversible are aliphatic, cycloketone, aldehyde, and nitrile derivatives. In another approach, 10 FDA approved drugs with CatL inhibitory activity have been suggested as safer and more efficient for prevention of SARS-CoV-2 cell entry and replication [173]. Among these are clofazimine, rifampicin, saquinavir, astaxanthin, dexamethasone, clenbuterol and heparin. Moreover, Ddec-RVKR-CMK (ecanoyl-Arg-Val-Lys-Arg-chloromethylketone) has previously shown inhibition of MERS-CoV entry [154], while EST [(23,25) trans-epoxysuccinyl-l-leucylamindo-3-methylbutane ethyl ester] [155], MDL-28170 (calpain inhibitor III, or *Z*-Val-Phe-CHO) [156], oxocarbazate [157] and SSAA09E1 {[(Z)-1-thiophen-2-ylethylideneamino] thiourea} [158] can block SARS-CoV entry.

3.3. Immune pathways

By inhibiting the expression of STAT1-activated genes, SARS-CoV2 suppresses the signaling pathways regulated by IFN, a crucial cytokine, released by virus-infected cells to recruit adjacent cells to boost anti-viral immune responses [174]. In the light of this, genes from a subset of IFN activated genes (IFIT1, IFITM1, IRF7, ISG15, MX1, and OAS2) have been identified as possible targets for COVID-19 therapy [175]. On the other hand, the strategy of combating excessive inflammatory responses often present in COVID-19 patients is to target a

critical regulator of cellular inflammation whilst keeping antiviral pathways unaffected [159]. Several drugs have been repurposed to act to the immune response and manage the cytokine storm induced by the viral infection. Some of these include tocilizumab and sarilumab (IL-6 receptor antagonists), which attenuate the inflammatory process by inhibiting IL-6 signaling. The JAK/STAT inhibitors fedratinib and ruxolinitinib attenuate cytokine storm, the S1Pr1 agonist fingolimod, diminishes cytokine storm, and infliximab and adalimumab block TNFα and decrease inflammatory processes [160]. Moreover, serine protease inhibitors inhibit NF-kb and decrease TNFα and IL-6 expression [160]. Anakinra is also used for inhibition of cytokines downstream of inflammasomes, including IL-1β, and has been subjected to phase III clinical trials for COVID-19 (www.clinicaltrials.gov, NCT04330638 and NCT04324021), [159]. Interim results from a phase III trial demonstrated a decrease in 28-day mortality and reduction in hospitalization [161]. Quercetin, an antioxidative flavonoid naturally present in plants, suppresses inflammasomes, including NLR family pyrin domain containing 3 (NLRP3), by decreasing ASC micrometer-sized structure production and oligomerization. Non-steroidal anti-inflammatory drugs (NSAIDs), particularly those of the fenemate class (*e.g.*, flufenamic acid), selectively inhibit NLRP3 by reversibly targeting volume-regulated anion channels that control Cl2 transport across the plasma membrane [159,161].

3.4. Hypoxia

COVID-19 hypoxia has a complicated etiology that encompasses thrombosis, pulmonary infiltration, viral invasion in pneumocytes, excessive cytokine secretion, dysregulated renin-angiotensin-aldosterone pathway, and inflammatory responses [176]. Hypoxia inducible factor-1 (HIF-1) controls cell proliferation, metabolism, and angiogenesis. It is released during immunological responses and plays crucial functions at the inflammation zone by encouraging the release of pro-inflammatory cytokines *via* immune cells [177]. HIF-1 also participates in the regulation of protein expression of key molecules of SARS-CoV-2 entrance, including ACE2 and TMPRSS2 on the cell surface [178]. Antioxidants have been suggested as a tissue barrier against reactive oxygen species (ROS) due to activation of immune cells, as well as suppressing HIF-1 driven cytokine secretion. Keeping in mind that the interaction of SARS-CoV-2 with endothelial cells, iron metabolism, and erythrocytes, as well as the resultant hypoxia, may lead to a number of coagulopathies, heparins are being commonly used for the treatment of COVID-19 patients. For example, a clinical trial in critically ill COVID-19 patients receiving a therapeutic-dose of heparin for anticoagulation did not improve survival rates [162]. In contrast, heparin treatment of non-critically ill COVID-19 patients increased survival and reduced the need of cardiovascular and respiratory organ support [163]. Concurrent inflammasome hyperactivation, especially in the context of hypoxia, is yet another prothrombotic mediator [164]. Melatonin has also been shown to prevent to some extent hypoxia, ferroptosis, and hemoglobin denaturation [164].

3.5. Calcium signaling

Calcium (Ca2+) is necessary for SARS-CoV fusion with host cells, suggesting that Ca2+ plays an important role in viral diseases [179]. SARS-CoV is also known to cause selective changes in Ca2+ signaling in host cells by activating Ca2+ channels and pumps and boosting intracellular Ca2+ load as part of reproduction, maturation, and survivability [180]. Changes in Ca2+ dynamics have been found to lead to alterations in numerous signaling pathways and gene functions. The voltage-gated calcium channel (VGCC) inhibitors, bepridil, amlodipine and nifedipine have been shown to diminish SARS-CoV-2 infection *in vitro* by preventing SARS-CoV-2 entry into host cells [165]. Vitamin D has been proposed to have a significant role in the control of autophagy or apoptosis through calcium signaling at the mitochondrial and ER levels during the COVID-19 pandemic. Vitamin D has also been demonstrated to down-regulate the toll-like receptors TLR2 and TLR4 in monocytes, resulting in reduced inflammatory reactions and stimulation of the synthesis of antimicrobial peptides (AMPs) such as defensin and cathelicidin, which may inhibit SARS-CoV-2. IROS production, oxidative stress, NADPH oxidase expression and DNA damage are also inhibited by vitamin D. Vitamin D stimulates the expression of antioxidant enzymes by upregulating a nuclear factor called erythroid-2(Nf-E2)-related factor 2 (Nrf2) [181].

3.6. Other pathways

3.6.1. Adaptor-associated kinase 1 (AAK1) and cyclin G-associated kinase (GAK)

The ACE2 receptor has several regulators, for example two cellular kinases from the serine–threonine protein-protein kinase family, AP2-associated protein kinase-1 (AAK1) and cyclin G-associated kinase (GAK), which mediate clathrin-dependent endocytosis [182]. Both AAK1 and GAK, have been linked to viral entry, assembly, and release [183]. AAK and GAK function as key regulators of the clathrin-associated host adaptor proteins and regulate the intracellular trafficking and clathrin-mediated endocytoses of multiple unrelated RNA viruses. Baricitinib was identified to possess a particularly high affinity for AAK1 and GAK, decreasing acute respiratory distress syndrome in patients and preventing SARS-CoV-2 from target cell entry and intracellular assembly [184]. Baricitinib is also capable of dampening the inflammation through JAK1/2 inhibition [185], and along with fedratiniband ruxolitinib, has been suggested to be effective against elevated levels of IFN-γ [186]. Although baricitinib, sunitinib and erlotinib possess similar JAK inhibitor potency, the high affinity of baricitinib for AAK1 suggests it to be superior in the group, especially given its once-daily oral dosing and acceptable side-effect profile [186]. As a result, it is advised that baricitinib should be tested on COVID-19 patients in order to minimize viral entrance and inflammation (NCT04321993). Other GAK kinase inhibitors include sunitib, and erlotinib, which also interact with AAK1, AXL, JAK1 and KIT. The interaction takes place with tyrosine kinase in the case of sunitib and for erlotinib with Abl1 [177]. However, sunitinib and erlotinib would be difficult for patients to tolerate at doses required for inhibition of AAK1 and GAK [187].

3.6.2. Phosphatidylinositol 3-phosphate 5-kinase (PIKfyve) and two-Pore Channel (TPC2)

Since endocytosis is an alternative mode of viral entry into host cells, phosphatidylinositol 3-phosphate 5-kinase (PIKfyve) is required during SARS-CoV-2 infection through the endocytic pathway [188]. This initiates phosphoinositide synthesis to regulate the formation of early endosomes. Apilimod, a PIKfyve inhibitor, is currently undergoing clinical trials (NCT04446377) for management of COVID-19 [166]. Though apilimod may reduce viral infiltration by suppressing host cell proteases, these enzymes are required for antigen presentation and T cell activation, and it has been suggested that apilimod might inhibit antiviral immune responses [189]. Furthermore, the two-pore segment channel (TPC2) activated by phosphoinositides in membranes of lysosomes is essential for endocytosis [190]. Two-Pore Channels have been recognized as a specific targeting potential for preventing SARS-CoV-2 entry into host cells and inhibition of virus replication by impairing the fusogenic potential of the endo-lysosomal system and altering the normal trafficking [167]. Accordingly, a clinical trial is underway to evaluate the efficacy of the TPC2 antagonist tetrandrine in COVID-19 treatment (NCT04308317) [168]. The flavonoid naringenin, found in fruits, has also been identified as an inhibitor of TPCs [190]. Furthermore, TPC2 antagonists ned-19 and tetrandine were proposed as putative lysosomal activity antagonists, resulting in additional suppression of autophagy at the breakdown stage. Keeping in mind that lysosomal Ca2+ dynamics, especially lysosomal Ca2+ efflux channel TPC2, plays a critical role in viral entry, TPC2 inhibition has been shown to prevent

entry of SARS-CoV-2 [167].

4. Conclusions

Despite encouraging success in tackling the COVID-19 pandemic, especially by developing and applying efficient and safe vaccines for global mass vaccinations, there is a continuous demand on further development. Although some success has been seen for repurposed antiviral drugs such as RDV and FPV, drugs like HCQ and ivermectin have proven disappointing with hardly any difference to placebo in large well-designed clinical trials [54,55]. In contrast, monoclonal antibodies have demonstrated efficacy in treatment of COVID-19 patients [90], but the high costs have been discouraging for supporting mass distribution especially in developing countries. Oral administration of molnupiravir seemed initially like a major breakthrough in COVID-19 treatment, but more thorough clinical evaluation suggested that the reduced risk of hospitalization was only 30% [50]. On the other hand, an 89% reduced risk of hospitalization and death has been highly encouraging for paxlovid [56].

In the context of vaccines, initially more than 90% vaccine efficacy was achieved for both adenovirus- [102,105,109] and mRNA-based [121,126] COVID-19 vaccines against the original SARS-CoV-2 Wuhan strain. However, with the advent of several emerging SARS-CoV-2 S variants, there has been serious concerns about reduced vaccine efficacy. Booster vaccinations have provided a quick short-term solution, but obviously re-engineering of vaccines targeting the novel variants/mutants has been seen as one solution. Current vaccine development has almost uniquely focused on the SARS-CoV-2 S protein, which due to its surface location is a key target for novel mutations aiming at circumventing the vaccine protection. Therefore, future COVID-19 vaccine development should profit from engineering vaccines based on other SARS-CoV-2 targets and also aiming at several target simultaneously providing types of pan-vaccines.

Similarly, there is also a genuine need to expand the spectrum of COVID-19 drug targets. In this context, we have reviewed signaling pathways which are affected by SARS-CoV-2 infections. The biologically essential RAS presents interesting therapeutic possibilities for targeting COVID-19, especially related to viral entry and manipulation of ACE2 and TMPRSS2. The impact of protein transport by ER and Golgi trafficking can be highlighted by existing FDA-approved CatL inhibitors, which can be repurposed for SARS.CoV-2, but also the potential discovery of novel drug targets. Immune pathways represent a rich source for identifying inhibitors, which can reduce inflammation and diminish cytokine storm events. In the context of hypoxia, therapeutic anticoagulation therapy with heparin has been conducted in both critically and non-critically ill COVID-19 patients to investigate its effect on survival rates. Moreover, drugs affecting calcium and other pathways have been studied in search for novel drugs capable of reducing entry and replication of SARS-CoV-2.

In summary, major progress has been achieved. However, intensive research and development is required to keep up with the evolution of new SARS-CoV-2 variants and to be prepared for future emerging outbreaks.

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Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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