https://doi.org/10.1070/RCR4961

Molecular basis of COVID-19 pathogenesis

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The review summarizes the publications, available at the time it was written, addressing the chemical and biological processes that occur in the human body upon exposure to coronaviruses, in particular SARS-CoV-2. The mechanisms of viral particle entry into the cell, viral replication and impact on the immune system and on oxygen transport system are considered. The causes behind complications of the viral infection, such as vasculitis, thrombosis, cytokine storm and lung fibrosis, are discussed. The latest research in the field of small molecule medications to counteract the virus is surveyed. Molecular targets and possible vectors to exploit them are considered. The review is primarily written for specialists who want to understand the chains of activation, replication, action and inhibition of SARS-CoV-2. Due to the short period of such studies, the data on complexes of small molecule compounds with possible protein targets are not numerous, but they will be useful in the search and synthesis of new potentially effective drugs.
The bibliography includes 144 references.

Contents

The following designations and acronyms are used in the review:

ACE2 — angiotensin converting enzyme 2,
ADE — antibody-dependent enhancement,
ARDS — acute respiratory distress syndrome,
CoV — coronavirus,
FcR —Fc receptor,
IFN — interferon,
IFNAR — interferon alpha-receptor,
IgG — immunoglobulin G,
IgM — immunoglobulin M,
MERS — Middle East respiratory syndrome,
ORF — open reading frame,
PAMP — pathogen-associated molecular pattern,
RAS — renin – angiotensin system,
RBD — receptor-binding domain,
SARS — severe acute respiratory syndrome,
STAT — signal transducer and activator of transcription.

1. Introduction. Structure of the SARS-CoV-2 virus

Coronaviruses (CoV) are enveloped viruses with a single-stranded RNA genome.[1] Currently, four types of coronaviruses (α, β, γ, δ) have been identified, with only two of them occurring in humans: α-coronaviruses (HCoV-229E and NL63) and β-coronaviruses (MERS-CoV, SARS-CoV, HCoV-OC43 and HCoV-HKU1).[2] These viruses can cause respiratory, intestinal and neurological diseases and hepatic disorders.[3] At the end of December of 2019, patients with cough, fever and shortness of breath accompanied by acute respiratory distress syndrome (ARDS), caused by unidentified viral infection, were registered in Wuhan (China). The sequencing of the viral genome of five pneumonia patients admitted to hospitals on December 18 to 29, 2019, showed the presence of the previously unknown β-coronavirus strain in all patients.[4]

The detected new β-coronavirus has a 88% homology with the sequences of two bat coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, and approximately 79.5% and 50% homology with SARS-CoV and MERS-CoV.[4] The International Committee on Taxonomy of Viruses gave the new β-coronavirus the name 'SARS-CoV-2' and the disease caused by SARS-CoV-2 was later called COVID-19. Analyses of 10 genome sequences of SARS-CoV-2 taken from COVID-19 patients were

Received 1 May 2020

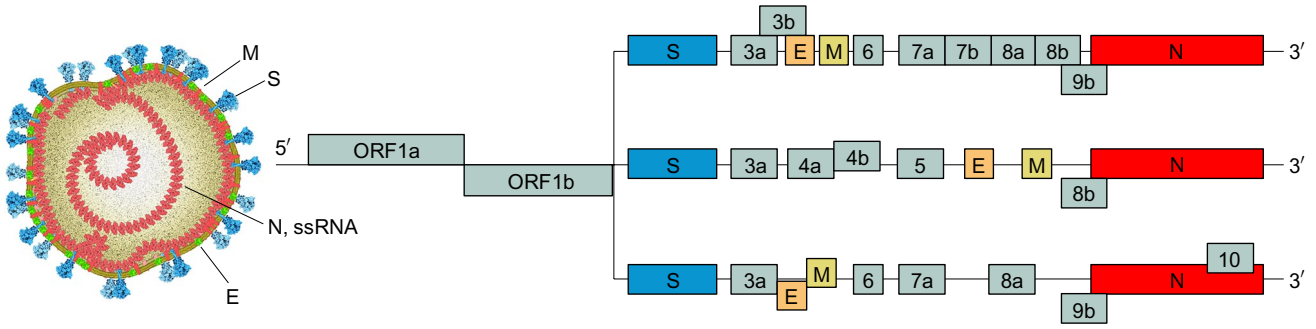

Figure 1. Structure of enveloped spherical particles of coronaviruses (100 – 160 nm in diameter). In SARS-CoV, MERS-CoV and SARS-CoV-2, two thirds of the genome encode polyproteins pp1a and pp1ab, which form the viral replicase – transcriptase complex. The other open reading frames in one-third of the genome encode four key structural proteins: spike glycoprotein (S), envelope protein (E), nucleocapsid protein (N) and membrane protein (M) and several auxiliary proteins not involved in replication.[10]

highly similar, demonstrating a more than 99.98% sequence homology;[4, 5] this indicates that the genome sequences of SARS-CoV-2 are highly conserved. It should be noted, however, that the data available to date are insufficient for the reliable conclusion on this issue.

Like other coronaviruses, the SARS-CoV-2 virion has a nucleocapsid, which accommodates the viral RNA and phosphorylated N protein.[6] The nucleocapsid is hidden inside phospholipid bilayers and covered by various types of proteins: the spike glycoprotein trimer (S) (spike protein, S protein), which is present in all types of CoV, haemagglutinin esterase (HE) and also a membrane protein (M) and an envelope protein (E), which are located between the spike (S) proteins in the viral envelope.[7]

The genome of SARS-CoV-2 resembles the genomes of typical CoV and contains at least ten open reading frames (ORFs). The first ORF (ORF1a/b) translates about two-thirds of viral RNA into two large polyproteins. In SARS-CoV and MERS-CoV, two polyproteins, pp1a and pp1ab, are converted to 16 non-structural proteins (nsp1 – nsp16),[8] which form the replicase – transcriptase complex.[9, 10] These nsp proteins restructure the rough endoplasmic reticulum (RER) membranes to double-membrane vesicles, in which the virus replication and transcription take place.[11] Other open reading frames of SARS-CoV-2, located on the remaining one-third of the genome, encode four main structural proteins: a spike glycoprotein, an envelope protein, a nucleocapsid protein and a membrane protein and several auxiliary proteins with unknown functions, which are not involved in virus replication[10] (Fig. 1).

Several research groups[12, 13] in China found that SARS-CoV-2, like SARS-CoV, enters the cells using the angiotensin converting enzyme 2 (ACE2). ACE2 is a type I membrane protein expressed in lungs, heart, kidneys and intestines, and mainly associated with cardiovascular diseases.[14] It is noteworthy that particularly these organs are the main targets for the coronavirus SARS-CoV-2.[15] Apart from cleavage of angiotensin (Ang) I to give Ang – (1 – 9), ACE2 also provides the direct binding site for the CoV spike proteins.[14] Coronavirus S protein consists of two subunits (S1 and S2) and exists in a metastable conformation, which undergoes a considerable restructuring to provide viral envelope fusion with the host cell membrane.[16] This process is triggered by linking of the receptor-binding domain (RBD) of the S1 subunit to the ACE2 receptor of the host cell. Linking of RBD to ACE2 initiates the endocytosis of the SARS-CoV-2 virion and subjects it to the action of proteases (mainly catepsin L and catepsin P), which leads to detachment of the S1 subunit and transition of the S2 subunit to a highly stable conformation. This promotes fusion of the viral envelope with the endosomal membrane and releases genetic material of the virus into the host cell cytoplasm.[16 – 19]

2. Pathogeneses of COVID-19

COVID-19 patients demonstrate the following clinical signs: fever (98% of patients),[20] non-productive cough (76%),[20] shortness of breath (> 50%) and myalgia and fatigue (44%)[20] and X-ray signs of pneumonia,[21] which resemble the clinical signs of SARS-CoV and MERS-CoV infections.[22] The average incubation period of the disease is 5.2 days (95% CI:† 4.1 – 7.0).[23, 24] Blood tests show a normal or reduced (25% of patients) white blood cell count and low lymphocyte count (65%).[21] In addition, pronounced macrophage and neutrophil infiltration is observed in lung biopsy samples.[25] Less frequent symptoms

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† CI is confidence interval.

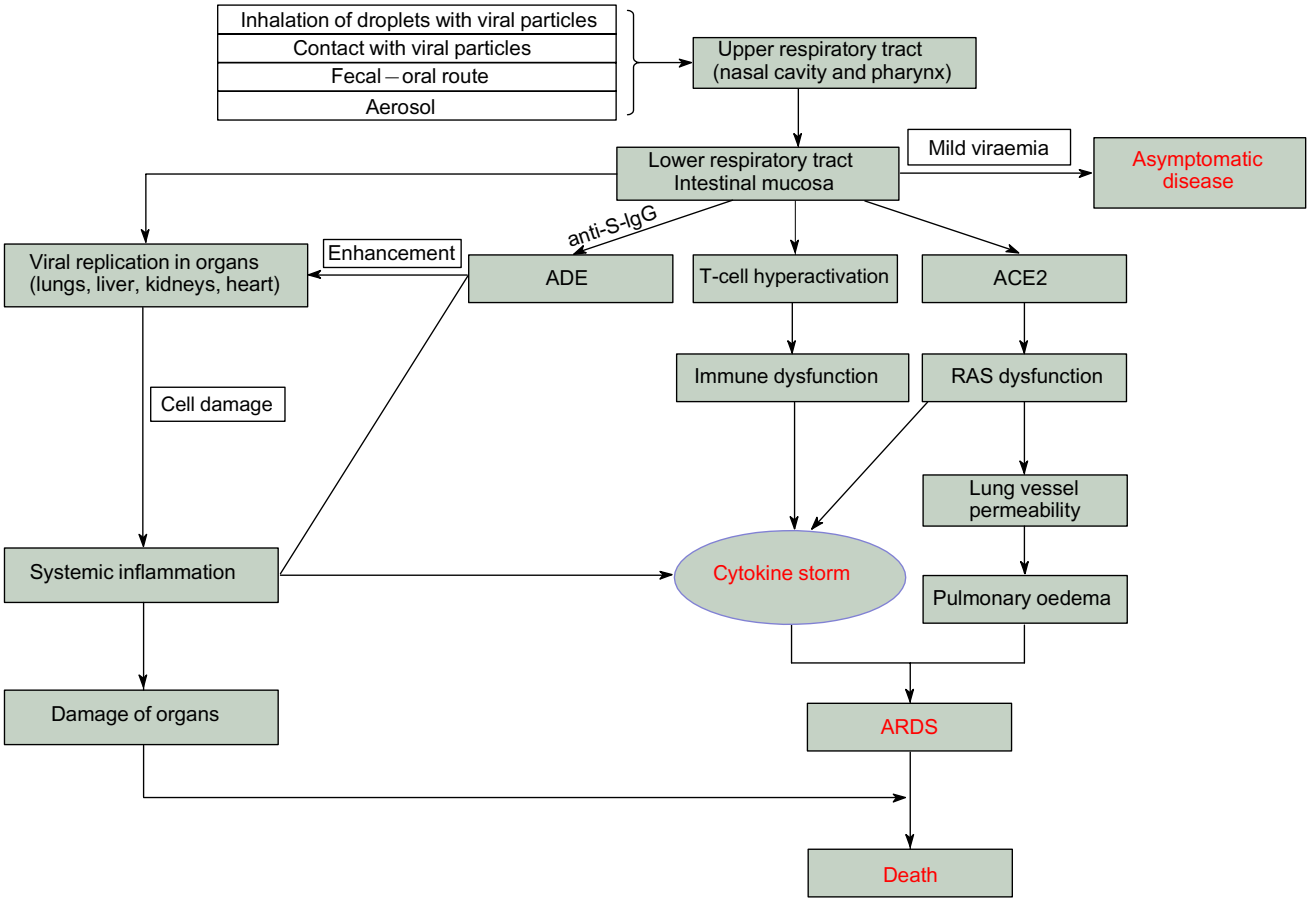


Figure 2. Pathogenesis of SARS-CoV-2 infection. ADE is antibody-dependent enhancement, ACE2 is angiotensin converting enzyme 2, RAS is renin–angiotensin system, ARDS is acute respiratory distress syndrome. The red colour marks important crisis points of SARS-CoV-2 infection.

include expectoration (28% of patients), headache (8%), blood spitting (5%) and diarrhea (3%). According to the data for hospitalized patients, it can be stated that in most cases (approximately 80%), COVID-19 goes without symptoms or as a mild disease, whereas the other 20% of cases develop severe (15%) or critical (5%) symptoms.[26,27] Currently, the lethality of COVID-19 is approximately 6.6% throughout the world; the death is mainly caused by the acute respiratory distress syndrome and development of multiple organ failure, especially in senior patients with diseases such as arterial hypertension, cardiovascular diseases and diabetes mellitus. Although the pathogenesis of COVID-19 is poorly studied, important information about the development of SARS-CoV-2 infection can be derived from similarity of the mechanisms of action of SARS-CoV and MERS-CoV (Fig. 2).

2.1. Coronavirus entry into the cell and replication

The coronavirus SARS-CoV-2 is mainly transmitted by inhalation of aerosol droplets bearing viral particles, or by direct contact of viral particles with respiratory or eye mucous membranes, and possibly by the fecal–oral route.[28] It is assumed that primary viral replication takes place in the epithelium of the mucous membrane of the upper respiratory tract (nasal cavity and pharynx), and then it is multiplied in the lower respiratory tract and the intestinal mucosa.[29] For this reason, direct antiviral therapy directed to destruction of viral particles on the mucosal surface of the upper respiratory tract (nasal cavity and pharynx) may prove to be efficient in the initial stage of the disease and in preventing severe forms of COVID-19.

It is important that fecal–oral infection gives rise to mild viraemia, and subsequent infection usually goes without symptoms or with moderate and non-respiratory symptoms. In the case of airborne infection, some patients also develop non-respiratory symptoms such as liver and heart damage, renal failure or diarrhea;[30–32] however, airborne transmission leads to a more severe disease, which often induces multiple organ failure.

The coronavirus S protein is an important determinant for virus entry into the host cell. This protein binds to its cell receptor, which is ACE2 for SARS-CoV (Ref. 10) and SARS-CoV-2;[17] CD209L (C type lectin, also called L-SIGN) for SARS-CoV;[18] and DPP4 for MERS-CoV.[13] The entry of SARS-CoV into the cells occurs apparently *via* endocytosis and the subsequent fusion of the viral envelope and the plasma membrane.[19] After endocytosis and formation of endosomes, the S protein of SARS-CoV is cleaved by lysosomal proteases (cathepsin L and cathepsin P), which results in fusion of the viral envelope with endosomal membranes and release of the viral RNA into the cytoplasm of the infected cell.[18,19] Therefore, cathepsin inhibitors (mainly cathepsin L and cathepsin P inhibitors) can

potentially be used for preventing the penetration of SARS-CoV-2 into host cells.

After fusion of the viral envelope with the endosomal membrane, the nucleocapsid enters the cytoplasm and releases the viral RNA into the cytoplasm; the RNA is translated into two polyproteins, pp1a and pp1ab, which are subsequently cleaved by intracellular proteases to give 16 non-structural proteins (nsp1 – nsp16); the latter form the viral replicase – transcriptase complex.[9,10] These nsp proteins convert the membranes of rough endoplasmic reticulum to double-membrane vesicles in which the replication and transcription of the virus take place.[9] The viral replication in double-membrane vesicles is an important mechanism, which allows the viral RNA to evade recognition by cell pattern recognition receptors and, hence, to prevent the cellular immune response in an early stage of infection.[5] The newly formed envelope glycoproteins are incorporated into the endoplasmic reticulum membrane or Golgi complex membrane, while the nucleocapsid is formed *via* combination of RNA and a nucleocapsid protein (N). Then the viral particles enter the endoplasmic reticulum – Golgi intermediate compartment (ERGIC). Finally, the vesicles containing viral particles fuse with the plasma membrane to release the virus.

It is noteworthy that ACE2 is widely expressed in the nosal mucosa, bronchi, lungs, heart, gullet, kidneys, stomach, bladder and ileum; therefore, all these human organs are vulnerable to SARS-CoV-2.[33] Lately, clinicians also suggested the potential pathogenicity of SARS-CoV-2 for testicular tissue, which brings about fertility problems in young patients.[34]

2.2. Humoral and cellular immunity

The replication of the coronavirus in double-membrane vesicles largely allows SARS-CoV-2 to avoid the recognition of viral RNA. However, after virus entry into the cell and replication, the viral antigens are presented to antigen-presenting cells, which are the core part of the antiviral immunity. The peptide fragments of the viral proteins are presented with the major histocompatibility complex (MHC) and are then recognized by virus-specific cytotoxic T-lymphocytes. The presentation of the SARS-CoV antigen depends mainly on MHC I molecules,[35] which are responsible for presentation of short peptide fragments. However, MHC II also promotes viral antigen presentation. The major histocompatibility complex proteins in humans are encoded by a DNA fragment called 'human leukocyte antigen' (HLA). Earlier studies demonstrated that polymorphisms in the HLA are correlated with the susceptibility to SARS-CoV; alleles such as HLA-B*4601, HLA-B*0703, HLA-DR B1*1202 (Ref. 36) and HLA-Cw*0801 (Ref. 37) are associated with high susceptibility to the infection, whereas the HLA-DR0301, HLA-Cw1502 and HLA-A*0201 alleles are associated with protection from SARS infection.[38] In addition, polymorphisms of the MBL (mannose-binding lectin) genes, providing antigen presentation, increase the risk of SARS-CoV infection.[39] In the case of MERS-CoV, the MHC II molecules such as HLA-DRB1*11:01 and HLA-DQB1*02:0 are also related to the susceptibility to the infection.[40]

The antigen presentation stimulates the humoral and cellular immunity of the body, which is mediated by virus-specific B- and T-cells. Similarly to common acute viral infections, the profile of anti-SARS-CoV antibodies shows a typical production pattern of immunoglobulins M and G (IgM and IgG). The SARS-specific IgM antibodies disappear by the end of 12th week after the onset of disease, whereas IgG antibodies can be retained for a long period, which indicates that particularly IgG perform the major protective function.[41] However IgG can be involved in antibody-dependent enhancement and thus facilitate the entry of the virus into host cells *via* Fc-receptor-mediated internalization. The involvement of IgG antibodies in antibody-dependent enhancement processes raises the question of whether they can be used for the therapy of the COVID-19 coronavirus infection (see Section 2.4).

The SARS-specific IgG are mainly antibodies against the S and N proteins of the virus.[42] Studies of the cellular immunity against coronavirus are more numerous than studies dealing with the humoral response. The most recent publications demonstrate that the level of CD4+ and CD8+ T-cells in the peripheral blood in SARS-CoV-2 patients is markedly reduced, as the cells themselves are hyperactivated, as indicated by the high proportion of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%).[43] It is worth noting that the decrease in the amount of T-cells is especially pronounced in elderly patients (above 60 years old) and patients in need of treatment in an intensive care unit.[44] The total amount of T-cells, like the amounts of CD8+ or CD4+ cells, is positively correlated with patient's survival.[44] According to statistical analysis, the amount of T-cells is also negatively correlated with the serum levels of interleukins IL-6, IL-10 and TNF-α. During the recovery, the concentrations of IL-6, IL-10 and TNF-α in patients are reduced and the T-cell level is restored. Finally, the T-cells in COVID-19 patients are characterized by markedly higher levels of the hyperactivation marker PD-1 in comparison with the control group. Furthermore, elevated expression of PD-1 and Tim-3 in T-cells can be seen during progression of the disease from the prodromal stage to the stage of pronounced symptoms.[44] Similarly, the acute stage of infection in SARS-CoV patients is associated with a considerable decrease in the T-cell level and their hyperactivation.

Furthermore, even in the absence of antigen, the memory T-cells (CD4+ and CD8+) can be retained over a period of four years in some patients who recovered from SARS-CoV, and they can induce T-cell proliferation, delayed type hypersensitivity response and γ-interferon (IFN-γ) production.[45] Six years after SARS-CoV infection, specific responses of T-cell memory to the peptide library of SARS-CoV spike protein could still be identified in 14 out of 23 recovered SARS patients.[46]

In a study[47] considering 99 disease cases in Wuhan, some of SARS-CoV-2 patients showed considerably increased total neutrophil counts (38% of the patients) and decreased total lymphocyte counts (35%) and also had increased serum levels of IL-6 (52%) and C-reactive protein (84%). In another study, it was found that intensive care patients have increased total neutrophil counts and decreased total lymphocyte counts compared to the patients who did not require intensive care. The extents of increase in the neutrophil count and decrease in the lymphocyte count were correlated with severity of the disease and the probability of death.[21,48] Thus, the therapy directed to decreasing the aberrant activation and chemotaxis of neutrophils represents a possible strategy for the treatment of severe cases of COVID-19. In addition, the patients in need of intensive care had higher levels of many cytokines: IP-10, MCP-1, MIP-1A and TNF-α.[21] These clinical details attest

to the possible involvement of hyperergic inflammation into progression and severe course of the disease. Similarly, an early and pronounced increase in the serum levels of pro-inflammatory cytokines was also observed in SARS-CoV and MERS-CoV infections, which attests to a similar pattern of aberrant inflammation caused by the cytokine storm.[49, 50]

2.3. Cytokine storm in COVID-19

The clinical presentation of the SARS-CoV-2 infection demonstrates a pronounced inflammatory response, resulting in uncontrolled pulmonary inflammation, which is likely to be the major cause of the lethal outcome, and in multiple organ damage, which is the second most frequent cause of death. A recent study[51] demonstrated that the SARS-CoV-2-induced uncontrolled pulmonary inflammation is associated with active viral replication, downregulation of ACE2 and antibody-dependent enhancement (ADE). It is noteworthy that SARS-CoV-2, like SARS-CoV, uses the ACE2 receptor to enter the cells; for this reason, both viruses affect similar cell populations.[52] The initial active viral replication causes mass death of epithelial and endothelial cells that express ACE2 receptors, which results in increasing vascular permeability and causes the aberrant production of pro-inflammatory cytokines and chemokines (Fig. 3).[53] Presumably, the loss of ACE2 function in lungs leads to increasing concentration of angiotensin II and to renin–angiotensin system dysfunction and additionally enhances the inflammation, which, in turn, promotes acute lung injury and development of the acute respiratory distress syndrome.[54]

It is noteworthy that overproduction of chemokines results in aberrant chemotaxis of immune system cells (predominantly monocytes, macrophages and neutrophils),[25] which easily get into the focus of inflammation because of the increased vascular permeability. Since monocytes and macrophages also express ACE2, these cells are targets for SARS-CoV-2.[55] In the focus of inflammation, monocytes, macrophages and neutrophils produce increased amounts of chemokines and also reactive oxygen species, which damage surrounding tissues and, in particular, destroy epithelial cells. The key role of macrophages in the development of the pathology is directly confirmed by a substantial increase in the amount of alveolar macrophages and even complete filling of some alveolar cavities with alveolar macrophages in autopsy samples of lungs of patients who died of COVID-19.[25] It was noted that generally the lymphocyte infiltration into the pulmonary tissue was much lower than the infiltration of macrophages, although some focal lymphocyte infiltrations were present in lungs.[25] Thus, the therapy directed towards decreasing the aberrant chemotaxis of immune cells (predominantly neutrophils, monocytes and macrophages) can act as a possible strategy for preventing severe cases of COVID-19 associated with ARDS.

The acute respiratory distress syndrome is a frequent immunopathological event for SARS-CoV-2, SARS-CoV and MERS-CoV infections.[56–58] Out of 41 SARS-CoV-2 patients hospitalized at the very beginning of the disease outbreak, six patients died of ARDS.[21] Apart from the renin–angiotensin system dysfunction, the uncontrolled excess inflammation (cytokine storm), caused by the release

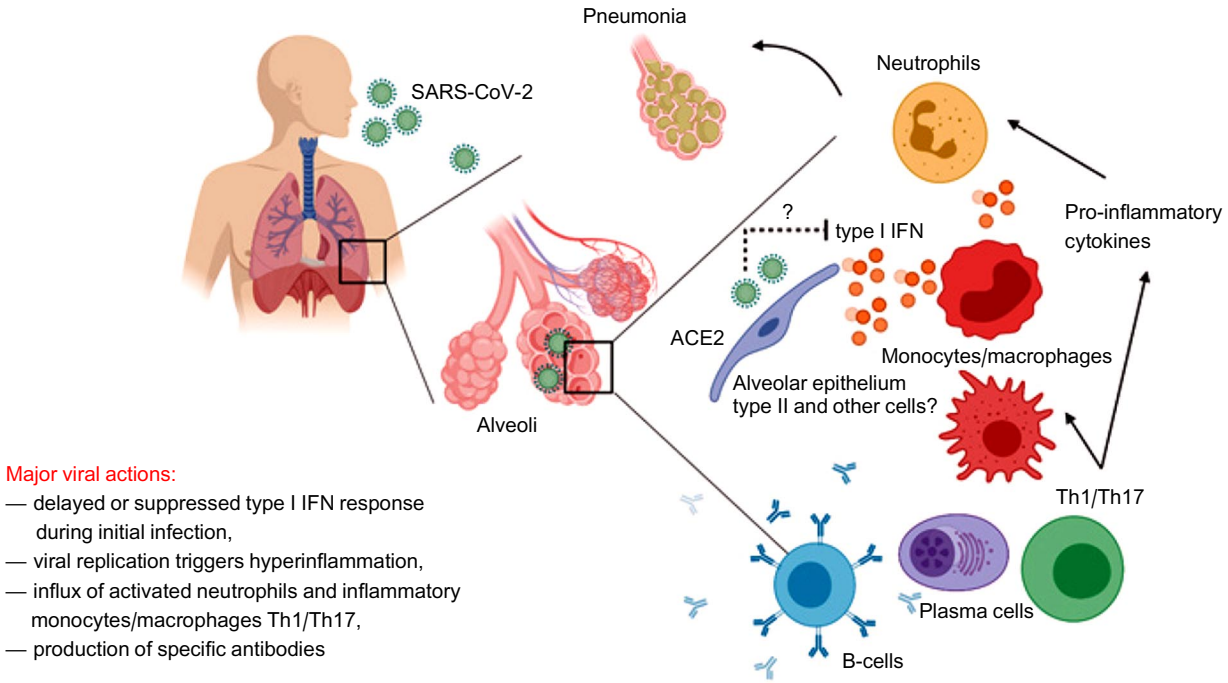


Figure 3. Putative host immune responses during the SARS-CoV-2 infection. Aerosol uptake of SARS-CoV-2 leads to infection of the target cells expressing ACE2 such as type 2 alveolar cells or other unknown target cells. The virus can dampen the antiviral responses of IFN, which leads to uncontrolled viral replication. The influx of neutrophils and monocytes/macrophages leads to hyperproduction of pro-inflammatory cytokines. The immunopathology of lungs may be due to the cytokine storm. Specific Th1/Th17 may be activated and contribute to enhanced inflammatory response. The B-cells/plasma cells produce SARS-CoV-2-specific antibodies, which can help to neutralize viruses. Reproduced with permission of *Asian Pacific Journal of Allergy and Immunology*, https://dx.doi.org/10.12932/AP-200220-0772.

of large amounts of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGF-β, *etc.*) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, *etc.*) by immune effector cells, is also a key factor for the development of ARDS in SARS-CoV patients.[26, 59, 60] Like SARS-CoV patients, those suffering from severe MERS-CoV infection have higher serum levels of IL-6, IFN-α, CCL2, CCL5, CXCL8 and CXCL-10 than the patients with mild or moderate course of the disease.[61] The cytokine storm causes a strong attack of the body by the immune system and development of ARDS and multiple organ failure and subsequently leads to fatal outcomes in severe cases of SARS-CoV-2, SARS-CoV and S-CoV infections.[43,62]

2.4. Antibody-dependent enhancement in COVID-19

The antibody-dependent enhancement (ADE) is a phenomenon in which viruses use the pre-existing non-neutralizing antibodies resulting from a previous infection to enter the host cells *via* Fc-receptor-mediated internalization. This phenomenon is well-known for the secondary infection with the Dengue virus (DENV), which causes a severe haemorrhagic disease.[63]

During the development of ADE, the pre-existing antibodies that appeared due to an earlier viral attack cannot neutralize the viral particles of the secondary infection with some antigenically related virus. Instead, IgG-opsonized viral particles act on the FcγR receptor expressed in endothelial and immune cells, thus facilitating virus attachment and entry into the cell. In addition, the intense replication of the virus may be followed by response of endothelial cells, increasing vessel permeability, which causes leukocyte extravasation and bleeding. On the other hand, monocytes become highly activated and can participate in the development of cytokine storm.[64]

Presumably, ADE is also typical of SARS-CoV-2 infection. As noted above, elderly (above 60 years of age) people are more susceptible to the infection for yet unknown reasons. Since coronaviruses are widely spread among the population all over the world, causing a mild infection and flu-like symptoms, seroconversion to the previously circulating coronaviruses is apparently widely encountered. Thus, it is reasonable to conclude that, for obvious reasons, elderly people were more often exposed to previous infections than younger people. This would imply a more extensive set of antibodies against coronavirus epitopes produced by long-lived plasma cells.

Since COVID-19 is not a haemorrhagic disease, it is likely that ADE, if present, is not mediated by endothelial cells. However, it has already been noted that pulmonary epithelial cells express FcγR2a.[65] Moreover, immune cells, including monocytes and dendrite cells, express this receptor to a high extent. Since the inflammatory infiltration of monocytes into lung tissue is one of the key pathogenetic factors of COVID-19 development, the monocytes that infiltrate lungs and express FcγR largely promote the replication of SARS-CoV-2 in lung tissue, which accounts for higher susceptibility of elderly patients. This hypothesis is confirmed by the fact that children and young adults do not belong to the risk group for this severe disease, which crucially differs from that caused by influenza virus.[66] In the context of ADE, it is reasonable to suggest that children, who were less, if at all, exposed to the previously spread coronaviruses, have a very limited set of IgG or only low-affinity IgM, which cannot induce ADE.

In addition, previous studies of MERS and SARS have already considered the possibility of ADE. A recent publication of Wan *et al.*[13] clarified the mechanism of ADE induction in human cells by monoclonal antibodies (mAb). It is of interest that mAb targeting the receptor-binding domain (RBD) of SARS and MERS proteins cause conformational changes in the protein, which are favourable for interaction with the dipeptidyl peptidase 4 (DPP4) receptor, a known receptor for MERS. Moreover, immune complexes also promote entry of the virus. Nevertheless, an increase in the antibody concentration suppresses viral invasion, as the RBD becomes inaccessible.

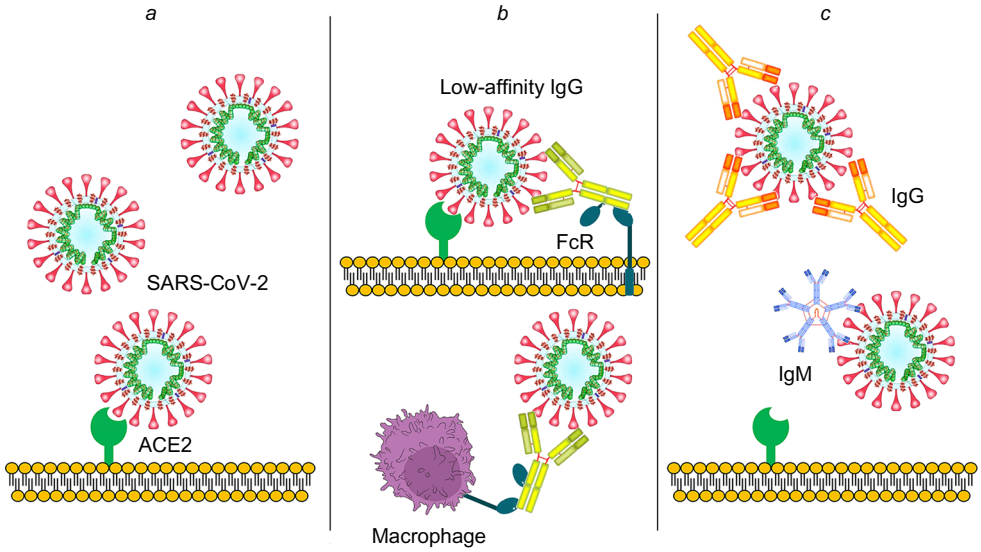


Figure 4. Illustrative scheme of ADE upon SARS-CoV-2 infection. (*a*) In the primary infection, the absence of pre-existing antibodies allows viral particles to interact with ACE2. (*b*) Existing low-affinity antibodies or antibodies at suboptimal concentrations bind to viral particles and facilitate FcR-mediated internalization in epithelial or immune cells. (*c*) Neutralizing IgG antibodies that appear after vaccination or neutralizing IgM do not enhance the binding to viral particles.[67]

This is in line with the data of Wang *et al.*,[67] who infected the HL-CZ promonocytic cell line, which expresses both ACE-2 and FcγR, with SARS-CoV in the presence of increasing concentrations of antibodies. It was found that, whereas higher antibody concentrations neutralized the virus, low concentrations induced ADE. Thus, as shown in Fig. 4, instead of neutralization of the currently circulating SARS-CoV-2, the pre-existing antibodies can bind to the viral particles and thus stimulate Fc-mediated internalization by the epithelial cells of lungs and infiltrating monocytes, thus impairing the condition of COVID-19 patients.

2.5. Mechanisms of coronavirus defence against immune response

There are several strategies used by SARS-CoV and MERS-CoV to better survive in host cells and evade immune responses (Fig. 5). This partly explains why coronavirus infections have, most often, longer incubation periods, on average 2 – 11 days, than influenza, where the incubation period is 1 – 4 days.[68] Longer incubation period is apparently caused by the ability of coronaviruses to evade recognition by the host immunity.

The evolutionary conserved microbial structures called pathogen-associated molecular patterns (PAMP), can be recognized by the pattern recognition receptors (PRR) TLR3 and TLR7 and by the cytosolic RNA sensor RIG-I/MDA5. This results in activation of the downstream signalling cascade, *i.e.*, NF-κB and IRF3, accompanied by their translocation into the nucleus. In the nucleus, these transcription factors induce expression of type I interferons (IFNs) and other pro-inflammatory cytokines; these primary responses form the first-line immune protection against viral infection in infected cells.[42] In turn, type I IFN activates the JAK-STAT pathway *via* IFNAR (type I interferon receptor), where JAK1 and TYK2 kinases phosphorylate STAT1 and STAT2. The STAT1/2 molecules form a complex with IRF9 and are together translated to the nucleus to initiate the transcription of IFN-stimulated genes (ISG).[42] The efficient innate immune response against viral infection considerably depends on the responses of the type I interferon and the downstream cascade, which ends in the control of viral replication and in induction of an efficient adaptive immune response. One of the mechanisms by which coronaviruses (MERS-CoV, SARS-CoV-2, SARS-CoV) combat the immune responses is associated with the action on MDA5 activation *via* direct interaction with the viral double-stranded RNA.[69] Furthermore, ORF4a, ORF4b, ORF5 and the membrane proteins of MERS-CoV inhibit the nuclear transport of the IFN regulatory factor 3 (IRF3) and activation of the IFN-β promoter.[70]

One more immune evasion mechanism used by SARS-CoV-2, SARS-CoV and MERS-CoV viruses is the production of double-membrane vesicles devoid of pathogen-associated molecular patterns, which are, therefore, not recognized by pattern recognition receptors. The virus successfully replicates in double-membrane vesicles and thus evades recognition of the viral RNA by the host.[11, 71]

In addition, SARS-CoV-2, SARS-CoV and MERS-CoV are likely to have direct inhibitory action on the expression of genes related to the antigen presentation.[72] Hence, activation of the expression of interferon-dependent genes and other approaches to dusrupt the immune evasion mechanisms used by SARS-CoV-2 are possible strategies for the treatment of COVID-19.

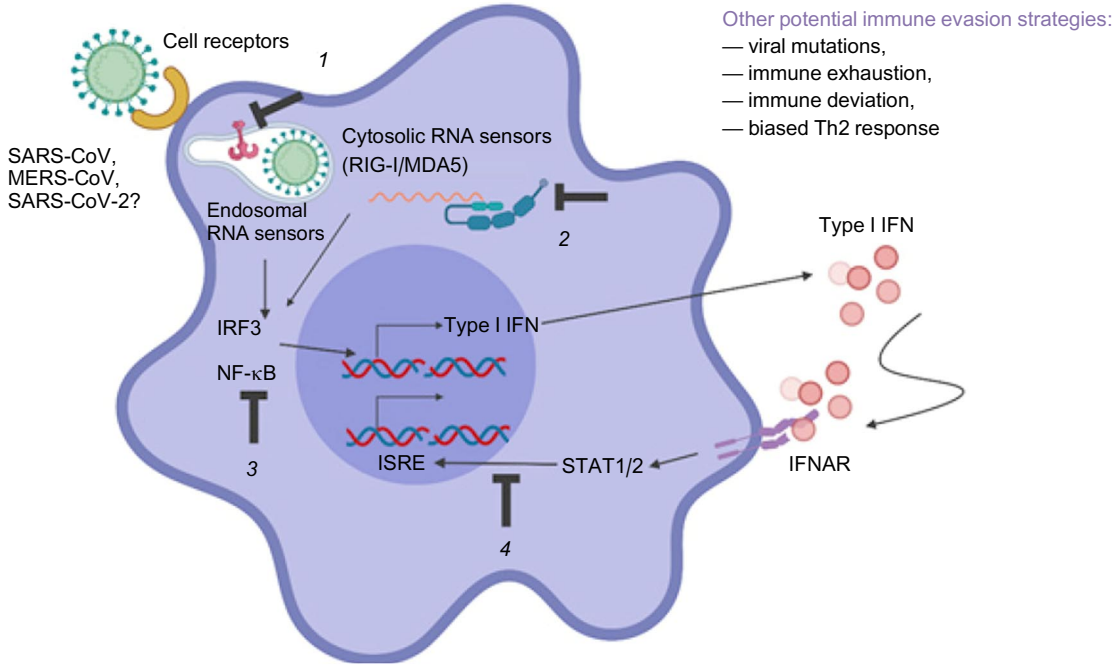


Figure 5. Potential immune evasion mechanisms common to SARS-CoV, MERS-CoV and SARS-CoV-2. Coronaviruses interfere at several stages in the initial innate immune response, including viral RNA detection (*1* and *2*), signalling pathway of type I IFN production (*3*), activation of STAT1/2 and IFN/IFNAR signal transducers (*4*). This delayed or dampened type I IFN responses affect the activation of adaptive immunity. Prolonged viral exposure enhances the inflammatory responses that may lead to immune exhaustion and immune suppression as a feedback regulatory mechanism. Reproduced with permission of *Asian Pacific Journal of Allergy and Immunology*, https://dx.doi.org/10.12932/AP-200220-0772.

2.6. Vasculitis and thrombosis in COVID-19

A characteristic clinical sign of COVID-19 in patients with severe form of the disease is the endothelial damage. Many critically ill patients had vasculitis-like symptoms or even the gangrene of the upper and/or lower extremities. A pathomorphological examination demonstrated that blood vessels of the alveolar septum were congested and oedematous, with moderate infiltration of monocytes and lymphocytes being present around the blood vessels. Small vessels showed hyperplasia, vascular wall thickening, lumen stenosis, occlusion and focal haemorrhage. In some of severe cases, hyaline thrombi of micro-vessels were observed.[43, 73, 74] Some patients had positive tests for antiphospholipid antibodies and high antibody titres, including anticardiolipin and anti-β2-glycoprotein antibodies, which was associated with severe thrombosis.[75] The cause behind the mechanism of vessel damage may be direct injury of endothelial cells by the virus, resulting in disseminated intravascular coagulation (DIC) syndrome, antiphospholipid syndrome (APS) and later in the development of vasculitis.

Apparently, signs of vasculitis (Fig. 6) may also be found in patients who had asymptomatic infection.[76] In particular, in Italy, an 'epidemic' of acute and spontaneously healing lesions of hands and feet was observed in asymptomatic children and adolescents. This vasculitis is not the only skin symptom of COVID-19; various types of rash and urticaria were also described. The signs of vasculitis are, most often, present in patients who have no other symptoms of the disease or several days after mild influenza symptoms. The vasculitis signs are accompanied by itching, burning, stiffness of joint movement in the case of hand lesions and pain in the case of foot lesions. The clinical signs affect feet or hands, most often one of them; they are multifocal and often asymmetrical, appear a few at a time in 2 – 3 days, and finally spontaneously disappear after 12 – 20 days.

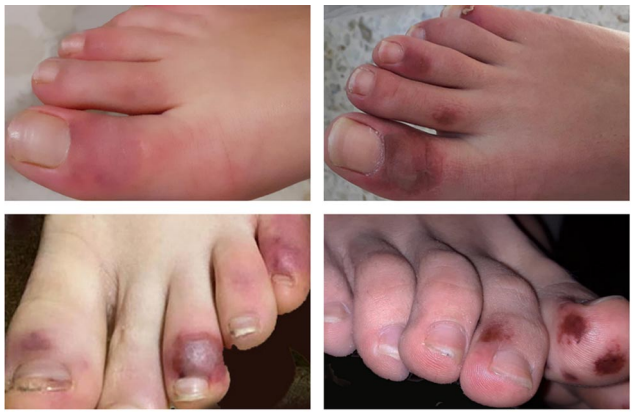


Figure 6. Clinical signs of vasculitis in asymptotic patients.[76] Reproduced with permission of *Eur. J. Pediat. Dermatol.*

2.7. Effect of SARS-CoV-2 on the oxygen transport system

Red blood cells are highly involved in the pathophysiology of COVID-19. In particular, reduced red blood cell counts are found in humans and some animals infected with SARS-CoV-2.[77] Furthermore, the severity of the disease is correlated with the red cell distribution width (RDW),[78] which reflects the size nonuniformity of the red blood cell (RBC) population in test samples. Since the red blood cell volume decreases with time, the increase in the RDW correlates with decreasing RBC turnover.[79] A decrease in the RBC turnover may be indicative of erythropoietic distress and serve as a compensatory mechanism for maintaining the level of circulating RBCs.[79]

The susceptibility to SARS-CoV-2 infection is apparently determined by the blood group; blood group A(II) is most susceptible to SARS-CoV-2 infection, whereas group O(I) is apparently less susceptible.[80] This result is consistent with previous studies, indicating that the susceptibility to the SARS-CoV strain of 2003 was determined by the blood group.[81] According to tentative data, CD147 (determinant of the Ok blood group system) binds the spike protein of SARS-CoV-2.[82] Blockade of CD147 disrupts normal RBC recirculation.[83] Post-mortem examination of COVID-19 patients demonstrated that the spleen was markedly shrinked. The decrease in the spleen size may be attributable to complete elimination of the RBC store as a normal physiological response to anemia.[84]

The primate models of COVID-19,[77] as well as studies of COVID-19 patients, show a decrease in the haemoglobin level[47] and increase in the total serum bilirubin and ferritine.[47] In general, these effects are similar to the signs of acute porphyria[85, 86] and are related to inefficient erythropoiesis,[87] fast turnover of haemoglobin and haem dissociation to release iron. Most recent studies demonstrate that a possible mechanism of haem dissociation is associated with the attack of porphyrin by the ORF8 protein (open reading frame 8 product).[88] Thus, SARS-CoV-2 jeopardizes the ability of red blood cells to transport oxygen, thus complicating maintenance of the normal partial pressure of oxygen in alveoli (PaO2).

In addition, it is assumed that SARS-CoV-2 directly affects the haem production,[88] which is confirmed by empirical data on the decrease in the haemoglobin level in COVID-19 patients[47] and using animal models of the disease.[77] The decrease in the haem production weakens the repression of the aminolevulinic acid synthase (ALAS) gene and thus increases the production of haem precursors, which results in accumulation of intermediate toxic porphyrin metabolites.[85]

It is noteworthy that SARS-CoV-2 symptoms and signs have much in common with those of acute porphyria. The overproduction of haem precursors such as aminolevulinic acid (ALA) and porphobilinogen (PBG) is manifested as life threatening episodes[89] and neurovisceral symptoms,[85] including abdominal pain (85% – 95% of cases), vomiting (43% – 88%), constipation (48% – 84%), muscular weakness (42% – 60%), extremity pain, headache, neck and chest pain (50% – 52%), hypertension (36% – 54%), tachycardia (28% – 80%), convulsions (10% – 20%), sensitivity loss (9% – 38%), fever (9% – 37%), respiratory muscle paralysis (5% – 12%) and diarrhea (5% – 12%). The neurotoxicity of aminolevulinic acid accounts for numerous neurovisceral symptoms. Furthermore, the neurovisceral signs of excess ALA largely coincide with the extrapulmonary symptoms in critical COVID-19 patients.

Thus, a pathogenetic feature of the COVID-19 infection is the action on the oxygen transport system. Apparently, SARS-CoV-2 causes depletion of the RBC pool as a result of binding of viral particles to the CD147 protein, which disrupts RBC recirculation. In addition, SARS-CoV-2 causes a decrease in the haemoglobin concentration and iron cleavage from the haem and directly diminishes the haem production.

2.8. Role of macrophage infiltration in the generation of fibrosis in COVID-19

As noted above, overproduction of cytokines and chemokines results in aberrant chemotaxis of immune cells (mainly monocytes, macrophages and neutrophils),[25] which get without obstacles into lung tissue. This results in a considerable increase in the amount of alveolar macrophages and even complete filling of some alveolar cavities with alveolar macrophages, which was found in autopsy samples of COVID-19 patients.[25] Alveolar macrophages express the ACE2 receptor, which is used by the SARS-CoV and SARS-CoV-2 coronaviruses to enter the cells. The RNA of SARS-CoV was found in alveolar macrophages;[90] furthermore, incubation of various immune cells (monocytes, macrophages, T- and B-lymphocytes) with the SARS-CoV-2 spike protein demonstrated that the viral protein binds to monocytes and macrophages but not to T- or B-lymphocytes.[25]

These data shed light on the role of macrophages as direct host cells for SARS-CoV-2 and potential drivers of the cytokine storm syndrome in the COVID-19 infection. The unusual aggregation and activation of alveolar macrophages can occupy the central position in the pathogenesis of severe cytokine storm in COVID-19 patients. It is important that development of COVID-19 infection leads to infiltration and activation of M2 phenotype alveolar macrophages, which in turn leads to increasing production of IL-5 and IL-13.[91]

The increase in the vascular permeability and damage of epithelial and endothelial cells give rise to a 'blood lake' in lung tissue and thrombin activation by tissue factors.[25] The activated thrombin cleaves fibrinogen to give fibrin, which is cross-linked to a polymer matrix (fibrin network) under the action of factor XIIIa derived from activated macrophages. Since high levels of IL-13 suppress the expression of tissue plasminogen activator (tPA), the lung tissue of COVID-19 patients possesses a reduced fibrinolytic activity and cannot cleave the formed fibrin polymer matrix. In turn, the formation of fibrin matrix enhances the inflammatory response, increases the production of IL-5 and IL-13 and other Th2 cytokines. The formation and growth of fibrin matrix accompanied by infiltration of various cells of the immune system form the basis for the development of lung fibrosis, one of the most severe COVID-19 complications.

3. Clinical trials

Before proceeding to analysis of the results of clinical trials, we would like to pay attention to publications addressing the development of a COVID-19 vaccine. Israeli scientists[92] reported a vaccine prototype preventing the infection and development of COVID-19.[92] According to the press release, the vaccine is a chimeric protein of one of the Nsp nonstructural proteins and the spike protein. The vaccine is planned for oral administration and will be available for *in vivo* testing in August, 2020. Meanwhile, it was reported[93] that the USA vaccine will be ready for mass production by January, 2021. Interestingly, back during the development of a vaccine against MERS,[94] it was shown that apart from the most reasonable use of the receptor-binding domain as a source of epitopes, the neutralizing antibodies binding other spike protein sites are also efficient.

The data on the current clinical trials of the drugs proposed for treatment of COVID-19 are summarized in Table 1.

Table 1. Clinical trials of drugs for the treatment of COVID-19.

Drug name (given by the developer)	Developer	Mechanism of action	Clinical trial phase	Information source[a]
Ruxolitinib	Incyte Corporation/ Novartis	Janus kinase 1 and 2 inhibitor	III	NCT04377620
Dapagliflozin	AstraZeneca	SGLT2 inhibitor (Sodium-glucose transporter 2), diabetes	III	NCT04350593
Tocilizumab	Roche	Immunodepressant; interleukin 6 receptor antagonist	III	NCT04363736
Anakinra	Swedish Orphan Biovitrum	Immune modulator; interleukin 1 receptor antagonist	III	NCT04324021
Tradipitant	Vanda Pharmaceuticals	Neurokinin 1 receptor antagonist	III	NCT04326426
Favipiravir	FUJIFILM Toyama Chemical	RNA replication inhibitor	III; approved for the therapy of COVID-19[b]	NCT04358549
Levilimab	Biocad	Treatment of rheumatoid arthritis; interleukin 6 inhibitor	III; approved for the therapy of COVID-19[c]	NCT04397562
CD24Fc	OncoImmune	Interleukin 1 beta inhibitor; interleukin 6 inhibitor, tumour necrosis factor alpha	III	NCT04317040
Metenkefalin/ tride cactide	Farmacija	White blood cell stimulator; opioid delta-receptor agonist; Th1 cell modulator	II/III	NCT04374032

Table 1 (continued).

Drug name (given by the developer)	Developer	Mechanism of action	Clinical trial phase	Information source [a]
Leronlimab	CytoDyn	CCR5 receptor antagonist; inhibitor of virus internalization	II/III	https://adisinsight.springer.com/drugs/800011544
Vazegepant	Biohaven Pharmaceuticals	CGRP antagonist	II/III	NCT04346615
Sarilumab	Regeneron/Sanofi	Interleukin 6 receptor antagonist	II/III	EudraCT2020-001162-12
Emapalumab	Swedish Orphan Biovitrum	Gamma-interferon inhibitor	II/III	NCT04324021
Alpha 1 antitrypsin-modified process	Grifols	Immune modulator; serine endopeptidase inhibitor	II	EudraCT2020-001391-15
Peginterferon lambda-1a	Eiger BioPharmaceuticals	Interleukin 29 receptor antagonist	II	NCT04331899
Ibrutinib	Janssen/Pharmacyclics	Agammaglobulinaemia tyrosine kinase inhibitor; emt-tyrosine kinase inhibitor	II	NCT02351037
AT 001	Applied Therapeutics	Aldose reductase inhibitor	II	NCT04365699
Clazakizumab	Vitaeris	Interleikin 6 inhibitor	II	NCT04343989
Plitidepsin	PharmaMar	Apoptosis stimulator; cell cycle inhibitor; protein synthesis inhibitor; VEGF-1 antagonist	II	See [95]
Selinexor	Karyopharm Therapeutics	Exportin-1 protein inhibitor	II	NCT03955783
GBV 006	Stanford University School of Medicine	Inhibitor of virus internalization; viral replication inhibitor	II	https://adisinsight.springer.com/drugs/800047635
LY 3127804	Eli Lilly	Angiopoietin-2 inhibitor	II	NCT04342897
HuMax IL8	Bristol-Myers Squibb/Gen mab	Interleukin 8 inhibitor	II	https://adisinsight.springer.com/drugs/800018226
Ad5 nCOV	Tianjin CanSino Biotechnology	Immunostimulator	II	NCT04341389
Gimsilumab	Kinevant Sciences	GM-CSF antagonist; GM-CSF receptor antagonist	II	NCT04351243
ASC 09/Ritonavir	Ascletis Pharmaceuticals	P450 inhibitor; HIV protease inhibitor	II	https://adisinsight.springer.com/drugs/800057510
Aviptadil	Relief Therapeutics Holdings	Vasoactive intestinal ppolypeptide receptor agonist	II	NCT04360096
Elsulfavirine	Viriom	Reverse transcriptase inhibitor	II	https://adisinsight.springer.com/drugs/800031212
APN 01	Apeiron Biologics	ACE stimulator	II	NCT04287686
DAS 181	Ansun Biopharma	Inhibitor of virus internalization	II	NCT04354389

[a] The column contains identifiers of clinical trials presented in web resources https://clinicaltrials.gov/(the identifier starts with NCT) and https://www.clinicaltrialsregister.eu/(the identifier starts with EudraCT) and references to the AdisInsight database. [b] Approved by the Ministry of Health of the Russian Federation on May 29, 2020. [c] Approved by the Ministry of Health of the Russian Federation on June 6, 2020, for patients with severe course of the disease in the case of cytokine storm.

4. Modelling of ligand – target binding in the search for effective drugs

In the last Section of the review, we give an account of published data on the modelling of ligand – target biological activity both for existing drugs and for molecular design of new drugs. It is noteworthy that despite high research and publishing activity directed towards the search for a potential anti-COVID-19 drug, some authors [96] do not share the universal optimism, because pandemics occur regularly (*e.g.*, Ebola and Zika viruses), but actually effective medications are still lacking. However, the same authors believe that computational chemistry methods (for example, virtual screening and docking) could markedly accelerate the search for an effective drug.

Currently, a number of electronic resources are devoted to collection, arrangement and permanent updating of public data on the structure determination for proteins that constitute SARS-CoV-2; an example is a web resource [97] collecting direct links to modelling results. A recent publication [98] presents data of cryoelectron microscopy for the structure of the spike protein, which is an important fragment of the viral particle. There is a website meant for the search for COVID-specific data by means of machine learning algorithms and natural language recognition.[99] A web server was created [100] in which anyone can carry out docking of a compound from the database comprising 42 proteins, including 20 viral proteins and 22 human proteins involved in the viral infection.

Special mention should be made of the papers that describe the application of modern computer technologies for the wide coverage of viral proteins. A research team [101] from the University of Mainz (Germany) employed a combined approach consisting of virtual screening, molecular docking and analysis of results by machine learning methods to search for active compounds. The spike protein, the nucleocapsid protein and 2′-*O*-ribose methyltransferase were chosen as the targets. The researchers performed virtual screening of the drug database over the whole surface of the targets followed by treatment with a neural network trained using test data. This study resulted in prediction of several drugs with a potential activity towards each of the three targets. It is noteworthy that some of the molecules mentioned in this publication as being potentially active were also mentioned previously, but in relation to other molecular targets. For example, ergotamine named as a potential inhibitor of 2′-*O*-ribose methyltransferase was mentioned previously as an RNA-dependent RNA polymerase inhibitor.[102]

Shah *et al.*[103] carried out molecular docking of 67 antiviral drugs into 18 proteins of the SARS-CoV-2 virus. The main idea was to search for molecules that can interact simultaneously with several targets. The best results were obtained for methisazone.

Repositioning of known drugs, already tested for the undesired activity, may represent the only solution to the problem of sudden epidemics of infectious diseases, whereas the development of new medications, which takes a long time and is subject to inherent limitations and obligatory verification procedures, seems to be of little use if a therapy should be quickly developed and immediately used to treat large numbers of patients.

Duarte *et al.*[104] used an approach based on the data on transcriptional changes, induced by various drugs and transcriptional signature of A549 lung carcinoma cells infected with SARS-CoV-2, for the search for drugs throughout the whole range of potential drugs for the treatment of COVID-19. Twenty six drugs were selected and studied by molecular docking to find out whether or not the selected compounds can physically interact with the RNA-dependent RNA polymerase of SARS-CoV-2 or with the main proteases of the virus. The molecules chosen as repositioning candidates included FDA-approved drugs such as

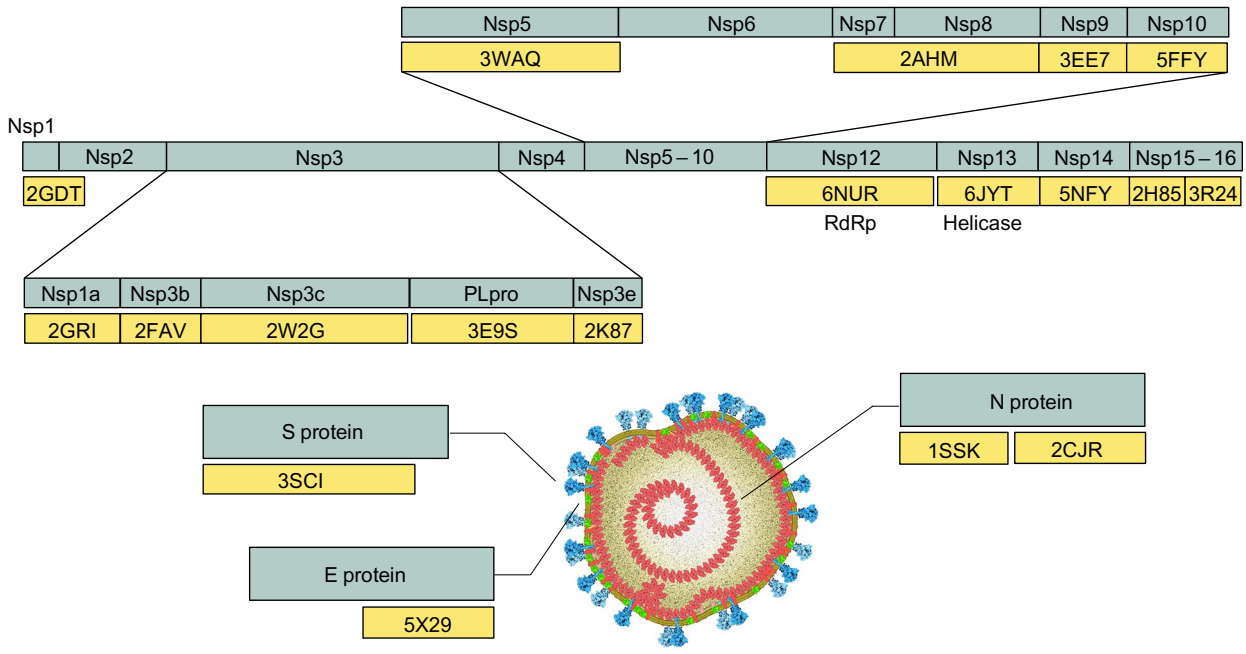


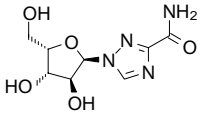
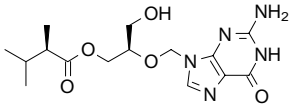
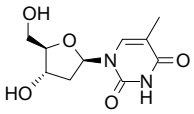
Figure 7. SARS-CoV-2 proteome map and coverage by experimentally permitted structures of MERS-CoV and SARS-CoV proteins with similar amino acid sequences.

flupentixol, reserpine, fluoxetine, trifluoperazine, sunitinib, atorvastatin, raloxifene, butoconazole and metformin.

Sonawane *et al.*[105] described the construction of a 3D model of the human serine protease TMPRSS2, which presumably participates in the fusion of a viral particle with a human cell *via* the interaction of ACE2 with the spike protein. By molecular docking, the authors demonstrated that the experimentally known inhibitors of this protease (camostat, nafamostat and bromhexine) efficiently bind to its active site.

Wu *et al.*[106] systematically analyzed all proteins encoded by the SARS-CoV-2 genes, compared them with the proteins of other coronaviruses and constructed 19 three-dimensional models by homology modelling (Fig. 7). The authors comprehensively considered the structures and screening results of important targets such as 3-chymotrypsin-like protease (3CL^{pro}), spike protein, RNA-dependent RNA polymerase (RdRp) and papain-like protease (PL^{pro}). As a result they chose a number of registered drugs that potentially inhibit the RdRp, PL^{pro} and 3CL^{pro} enzymes (Tables 2–4).[106]

Table 2. Potential PL^{pro} inhibitors with antiviral activity contained in the ZINC structural database (https://zinc.docking.org).

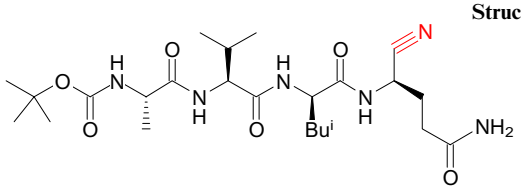
Compound	Structure
Ribavirin	
Valganciclovir	
β-Thymidine	

Despite the fact that the spike (S) protein is an important structural protein of a viral particle and participates in the attachment to the host cell, the search for small molecules that would directly affect the S protein appears to be a complicated, although highly attractive challenge. In this case, using the protein–protein docking, the researchers were able to show that the spike protein trimer can potentially interact with the human CD26 protein, which may be a factor of the virulence.[107]

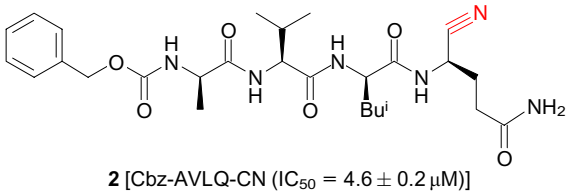
As has been noted above, coronavirus needs 3C-like protease 3CL^{pro} for proteolytic treatment of polyproteins and replication; hence, study of 3CL^{pro} is promising for the development of medications against the coronavirus infection.

In 2013, Chuck *et al.*[108] reported the synthesis of peptidomimetic inhibitors based on cyanamides with various peptide substituents in the α-position to the cyano group (structures **1** and **2**). The compounds were investigated for their inhibitory effect on the activity of SARS 3CL^{pro}. The IC_{50} values for the compounds were in the range of 4.6–49 μM, thus demonstrating that the cyano group can efficiently deactivate the autoprotolysis of 3CL^{pro}. The best inhibitor, Cbz-AVLQ-CN, was 10 times as efficient as other tested inhibitors. Studies of the crystal structures of enzyme–inhibitor complexes (compounds **3**) demonstrated that the cyano group of the 3CL^{pro} inhibitor forms a covalent bond with Cys145, whereas the AVLQ peptide interacts with the amino acid residues of the substrate-binding sites S1, S2 and S4 of 3CL^{pro} by forming hydrogen bonds. It was also shown that Cbz-AVLQ-CN inhibits 3CL^{pro} from strains of human coronaviruses 229E, NL63, OC43 and HKU1 and infectious bronchitis virus, with IC_{50} varying from 1.3 to 3.7 μM.

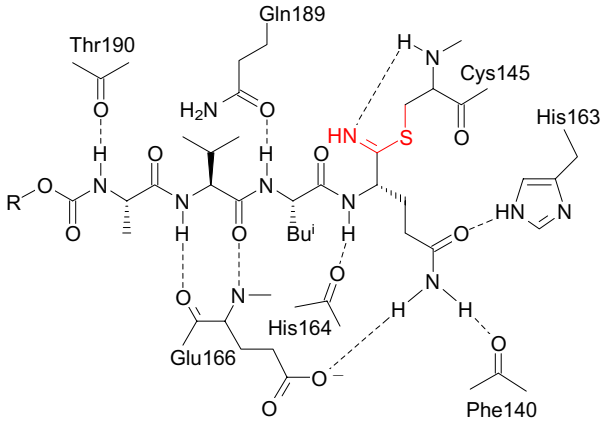
Structures 1–3



1 [Boc-AVLQ-CN (IC_{50} = 49 ± 2 μM)]



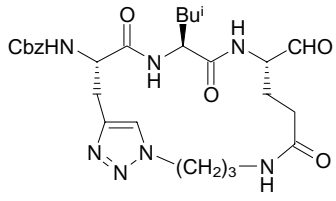
2 [Cbz-AVLQ-CN (IC_{50} = 4.6 ± 0.2 μM)]



3

In 2013, several macrocyclic protease inhibitors, including SARS-CoV 3CL^{pro} inhibitors (*e.g.*, compound **4**), were reported.[109] The *in vitro* efficiency against the coronavirus protease was moderate (15 μM), and this concentration cannot be attained *in vivo*.

Structure 4



4

Recently,[110] an attempt was made to find a potential drug against SARS-CoV-2 among natural compounds used in the traditional Chinese medicine. The amino acid sequence of 3CL^{pro} is highly conserved among coronaviruses, which allowed homology modelling of the three-dimensional structure of 3CL^{pro} of SARS-CoV-2 based on SARS-CoV (~96% sequence homology). The resulting

Table 3. Potential PL^{pro} inhibitors from natural sources.[106]

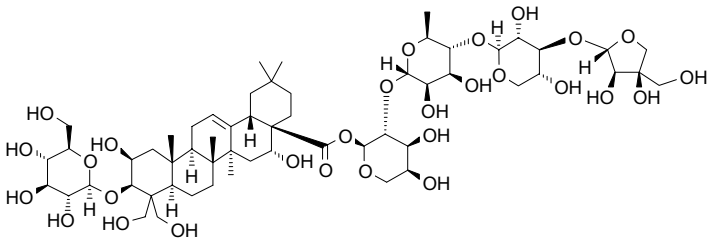
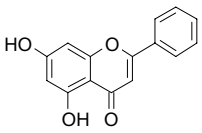
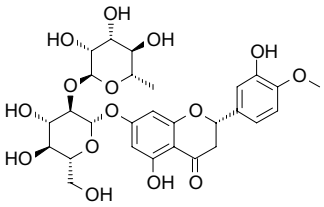
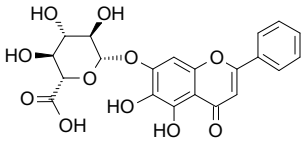
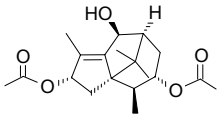
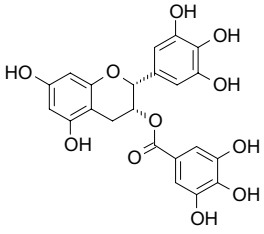
Name	Structure	Pharmacological action	Natural source
Platycodin D		Antitumour, anti-inflammatory	*Platycodon grandiflorus*
Chrysin		Antiviral, anti-inflammatory	*Scutellaria baicalensis*
Neohesperidin		Antitumour, antiallergic	*Citrus aurantium* L.
Baicalin		Antitumour, anti-inflammatory, antibacterial, antiviral	*Scutellaria baicalensis*
Sugetriol 3,9-diacetate		IgG antibodies against hepatitis B virus (HBV) and type 1 herpes simplex virus (HSV-1)	*Cyperus rotundus*
(−)-Epigallocatechin gallate		Antioxidant, antitumour action, antidepressant	*Camellia sinensis*

Table 4. Potential PL^{pro} inhibitors found by screening of the ZINC structural database (https://zinc.docking.org).

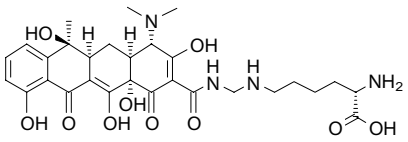
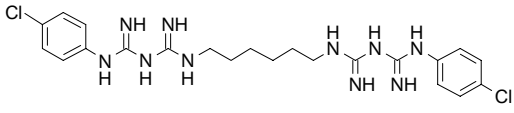
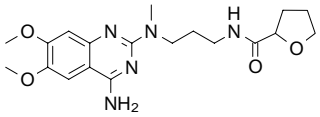
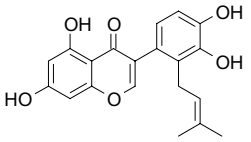
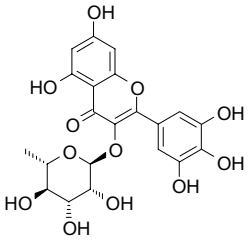
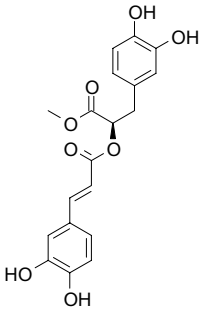
Name	Structure	Pharmacological action
Lymecycline		Antibacterial
Chlorhexidine		Antibacterial
Alfuzosin		Antihypertensive, treatment of benign prostatic hyperplasia

Table 5. Potential 3CL^{pro} inhibitors found by molecular modelling among the natural compounds encountered in traditional Chinese medicine.

Source of data	Name	Natural source	Structure
PubChem, 11610052	5,7,3′,4′-Tetrahydroxy-2′-(2-methyl-but-2-en-4-yl)isoflavone	*Psorothamnus arborescens*	
PubChem, 5281673	Myricitrin	*Myrica cerifera*	
PubChem, 6479915	Methyl rosmarinate	*Hyptis atrorubens* Poit.	

model was verified for the retention of spatial compatibility with several known inhibitors of SARS-CoV 3CL^{pro}; after that, several hit compounds were identified by virtual screening and additionally confirmed by molecular dynamics (Table 5). No experimental data on the activity of these compounds are available as yet.

Macchiagodena *et al.*[111] carried out a study with the goal to identify the similarity between 3CL^{pro} inhibitors for SARS-CoV and SARS-CoV-2. The similarity was very high, but this is not surprising, since the homology of the amino acid sequences of these proteins is 96.1%.

Yu *et al.*[112] described the application of molecular docking for the search of inhibitors of 3CL^{pro} viral protease among active natural compounds used in the traditional Chinese medicine. The flavonoid luteolin was named as a promising candidate; however, the authors note that they did not validate the result even by molecular dynamics.

Hall and Ji[113] also used homology modelling and molecular docking to find 3CL^{pro} and spike protein inhibitors among known drugs. Zanamivir, indinavir, remdesivir and sacvinavir were chosen as potential protease inhibitors. It is of interest that molecules well known for high binding affinity when docked into any site, that is, flavin adenine dinucleotide, nicotinamide adenine dinucleotide, coenzyme A, *etc.*, are the hit molecules for spike proteins. On April 30, 2020, EMA's (European Medicines Agency) Committee for Medicinal Products for Human Use (CHMP) started a 'rolling review' of data on the use of the investigational antiviral drug remdesivir (previously used in the treatment of Ebola) for the treatment of COVID-19; and on June 25, 2020, it recommended to grant a conditional marketing authorization to remdesivir for the treatment of COVID-19.

Zhang *et al.*[114] made an attempt to gain insight into the mechanism of action of a multicomponent medication of the traditional Chinese medicine called 'Respiratory Detox Shot'. Out of 1071 known compounds present as components of this medication, 157 compounds structurally resemble drugs and 48 show high binding energies to 3CL^{pro} according to docking results. Twenty two compounds were shown to inhibit 3CL^{pro} when present at concentrations of < 100 μM (the particular values are not given in the source).

In 2014, owing to the appearance of experimentally resolved three-dimensional structure of the papain-like protease PL^{pro} of MERS-CoV, Lei *et al.*[115] succeeded in analyzing its structural features, in particular, the unique structure of the oxyanion hole, differing from that in the characterized papain-like proteases. This structure of the viral protease served as the starting point for numerous studies aimed towards the search for enzyme inhibitors by computational chemistry methods.

A study[116] published in 2019 is devoted to high-throughput screening of a library comprising $\sim 30\,000$ compounds. As a result, two compounds inhibiting the protease with $IC_{50} = 20$ and 25 μM were selected (Fig. 8). The RNA-dependent RNA polymerase was not neglected either. The model of its potential 3D structure constructed by homology modelling was first reported by Lung *et al.*[117] Elfiky[118,119] analyzed the possible efficacy of nucleoside inhibitors of RNA-dependent RNA polymerase that had already been approved for the therapy of viral hepatitis C (Fig. 9). The authors modelled the 3D structure of RdRp of the SARS-CoV-2 virus and performed molecular docking to assess the binding of nucleoside analogues to it, which showed their potential efficacy. This information is evidently of certain value. However, the conclusion drawn in

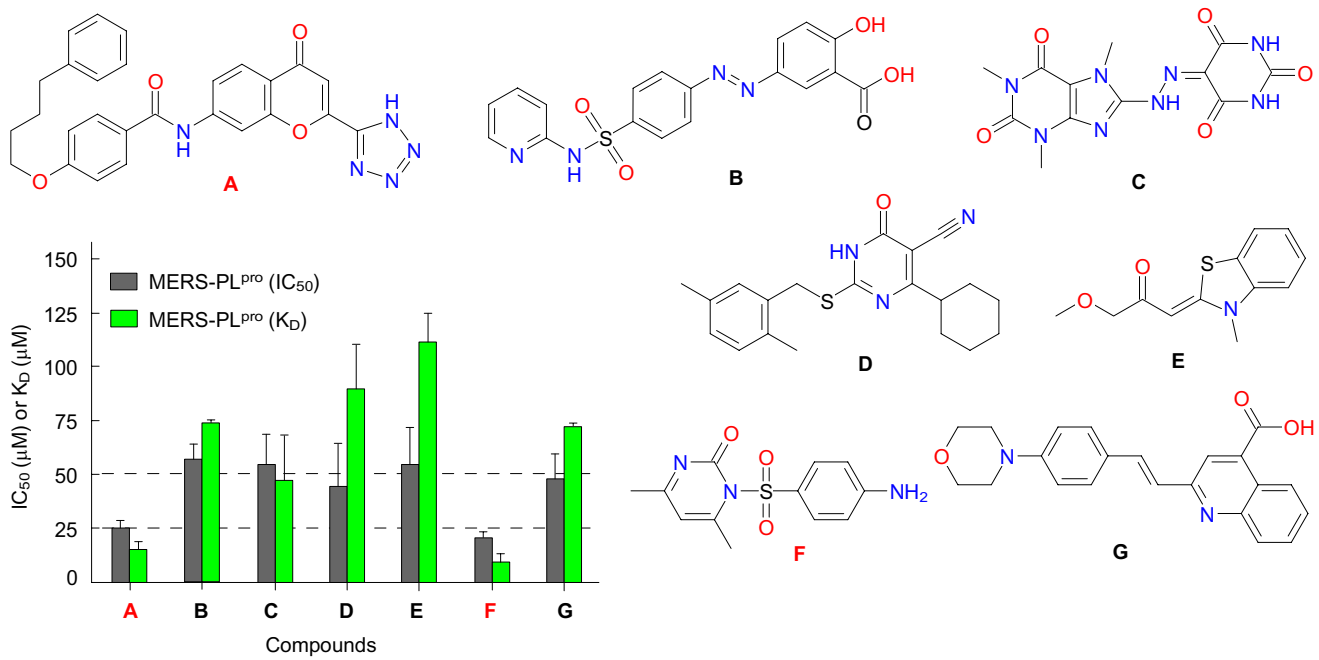


Figure 8. Examples of PL^{pro} inhibitors found by virtual screening.[116]

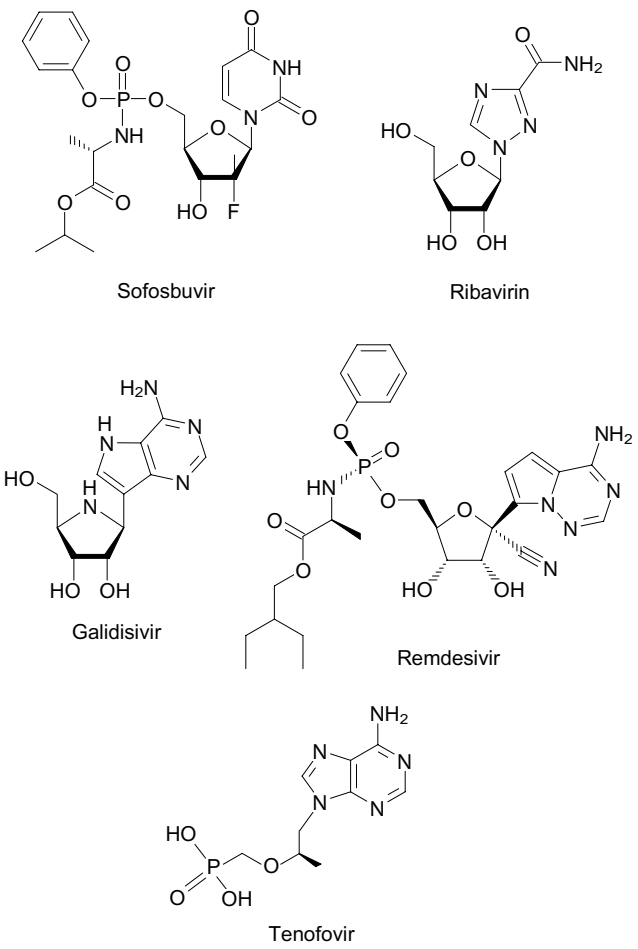
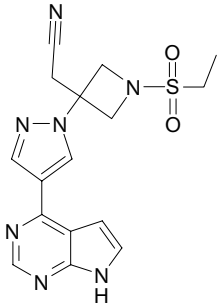


Figure 9. Nucleoside inhibitors of RNA-dependent RNA polymerase approved for the use against hepatitis C virus.

the study is rather trivial, because the homology of the amino acid sequences of SARS-CoV and SARS-CoV-2 RNA-dependent RNA polymerases is 90%, *i.e.*, differences between these structures, if at all present, are not large enough to be detected by docking. Meanwhile, despite the efficacy of already known antiviral agents of the same class (nucleoside analogues), no data on their successful use for the treatment of COVID-19 were reported as yet.

The limited available data on the pathogenesis of COVID-19 suggest a potential activity of some antirheumatic drugs, either acting as direct antiviral agents or targeting the host immune response.[120] The antirheumatic drugs of the 4-aminoquinolone group (*e.g.*, chloroquine), which are usually employed in rheumatology and as antimalarial drugs, can modify the lysosomal proteases that mediate the entry of the virus into the cell and have already shown efficacy against the coronavirus infection in clinical trials.[121] In some studies, it was shown that the level of cytokines IL-1 and IL-6 is positively correlated with the severity of the infection.[122] Drugs that block IL-1 and IL-6 may be effective,[123] as they prevent the development of the cytokine storm in severe cases; and tocilizumab showed good results in the treatment of a small number of patients.[94] Baricitinib (**5**), JAK1 and JAK2 kinase inhibitor possessing anti-inflammatory properties, is also considered

Structure 5



5 (Baricitinib)

as a medication for the treatment of COVID; however, the consequences of using this drug caused by blockade of the JAK/STAT signalling pathway can be ambiguous.[124] Ceribelli *et al.*[120] recommended that patients with rheumatic disease who take immunosuppressive drugs should maintain the chronic therapy, prevent infection by avoiding social contacts and stop taking the immunosuppressive drugs in the case of infection.

As noted above, the key route for the entry of viral particles into cells is internalization after direct binding to angiotensin-converting enzyme 2. Presumably, the action of ACE2 inhibitors could affect the development of the viral infection; however, currently researchers believe that patients with hypertension who take ACE2 inhibitors and angiotensin receptor blockers should not stop taking these drugs.[125]

Finally, mention should be made of the specific antiviral activity of orally available EIDD-2801 (N4-hydroxycytidine β-D-5′-isopropyl ester) against SARS-CoV-2, MERS-CoV, SARS-CoV and analogous bat-borne zoonotic CoV (group 2b or 2c). This compound is the prodrug of the ribonucleoside analogue EIDD-1931 (NHC, β-D-N4-hydroxycytidine).[126] These compounds also inhibit the resistance of coronavirus against the nucleoside analogue remdesivir (RNA-dependent RNA polymerase inhibitor).[126]

The action of the popular drug triazavirin and other factors of COVID-19 pathogenesis are covered in a review.[127]

Publications (see, *e.g.*, a review [128]) addressing modelling of the drug–target binding for the considered cases show that classical docking methods should be further developed in the following ways:

— scaling of the numbers of structures used for virtual screening and machine learning. For example, virtual screening of 1.3 billion compounds gives results on coronavirus inhibitors in line with experimental data.[129] The model for targeted synthesis obtained by deep docking is presented as ligand–target in the binding site of SARS-CoV-2 protease according to docking data (Fig. 10).[130] Similarly, a list of 9 compounds potentially active as M^{pro} inhibitors and natural compounds, (−)-taxifolin and rhamnetine, with the same action were selected out of 606 million structures using screening and molecular dynamics followed by expert analysis;[131]

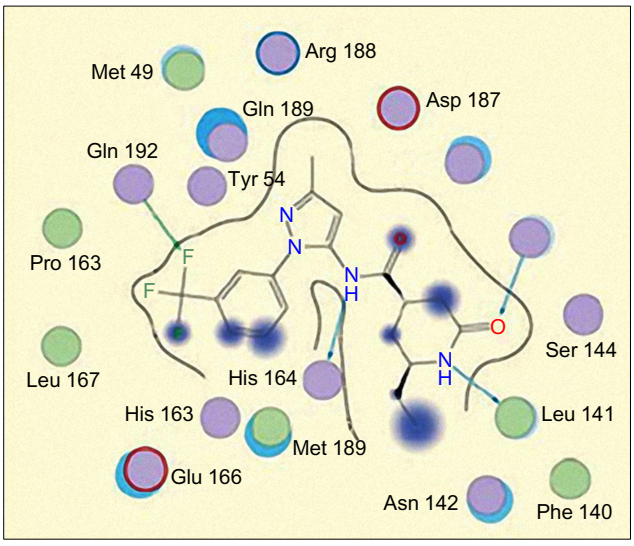


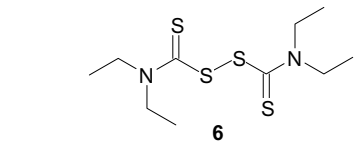
Figure 10. Structure of the potential SARS-CoV-2 protease inhibitor M^{pro} found by virtual screening of a library of 1.3 billion compounds.[130]

— improvement of approaches to clusterization of the results of virtual screening. For example, docking of a large number of small molecules and subsequent clusterization of the resulting structures gave new structural classes of inhibitors of poly(ADP-ribose)polymerase and CDK2 and EphA2 kinases (cancer treatment targets);[132–136]

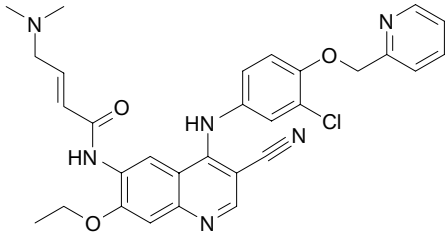
— using the free energy perturbation (FEP) method, which can take into account conformational changes and solvent effects [135] and which was successfully applied for modelling and targeted synthesis of Syk kinase inhibitors (for the therapy of rheumatoid arthritis);[136]

— using the on-top docking method, which takes into account non-specific interactions between the ligand and the protein surface. It was shown [137] that this extension of the classical docking method considerably increases the probability of exclusion of false-active ligands in the virtual screening for proteins having open active sites; these include $3CL^{pro}$ and other proteins, which are potential targets for combating SARS-CoV-2. For example, using on-top docking, potential $3CL^{pro}$ inhibitors were identified [138] in the database of FDA-approved drugs,[139] in particular disulfiram **6** (aldehyde dehydrogenase inhibitor) and neratinib **7** (kinase inhibitor) used as adjuvant therapy to treat the HER2-positive breast cancer. Molecular dynamic simulation demonstrated that these structures do not dissociate from the protease active site;[138]

Structures 6, 7



6



7

— active use of spectral data for precise positioning of the ligand–target pair;[140]

— calculation of transition states and dynamics of complexes of biologically active objects by quantum chemical methods.[141, 142]

Since the review addresses a subject with continuously updated information, the editors did a favour for the authors and allowed them to update the manuscript until it is sent for publishing. This part contains relevant information that appeared after the manuscript was written and before it was finally published.

A group of researchers from the USA, France and Switzerland reported [143] the discovery of multiple monoclonal antibodies binding the spike protein of SARS-CoV-2. The antibodies were identified in the memory B-cells of a person who was infected with SARS-CoV in 2003. The

antibody, which was called S309, efficiently neutralized the SARS-CoV-2 and SARS-CoV pseudoviruses and authentic SARS-CoV-2 by linking to the receptor-binding domain of the spike protein. Using cryelectron microscopy, it was shown that S309 recognizes the glycan-containing epitope, which is retained within the sarbecovirus subgenus, without competing with receptor binding.

Antibody cocktails, including S309 together with other identified antibodies, additionally enhance neutralization of SARS-CoV-2 and can restrict the appearance of resistant mutants. These results pave the road for using S309 and antibody cocktails containing it as a preventive treatment for persons at high risk of infection or as a post-contact treatment for the control or therapy of severe diseases.

5. Conclusion

The authors of the review support 'A Global Collaboration to Accelerate the Development, Production and Equitable Access to New COVID-19 diagnostics, therapeutics and vaccines' adopted by the World Health Organization.[144]

Several conclusions can be drawn from analysis of the published data:

— the SARS-CoV-2 coronavirus is mainly transmitted by inhalation of aerosol droplets bearing viral particles, or by direct contact of viral particles with respiratory or eye mucous membranes, and by the fecal – oral route.

— SARS-CoV-2 enters the cells using the angiotensin converting enzyme 2 (ACE2), which is widely expressed in the nasopharynx mucosa, bronchi, lungs, heart and blood vessels and in the gullet, kidneys, stomach, bladder and ileum. Therefore, the primary replication of the virus takes place in the epithelium of the mucous membrane of the upper respiratory tract (nasal cavity and pharynx), while further replication occurs in the lower respiratory tract and/or intestinal mucosa.

— It is important that the initial period of development of SARS-CoV-2 infection is characterized by low immune response associated with the ability of the coronavirus to evade recognition by the host immunity by suppressing the activation of cellular immunity, inhibiting expression of the genes associated with presentation of the antigen and evading the detection by pattern recognition receptors. This promotes fast replication of the virus in the initial stages of the infection.

— The initial fast replication of the virus causes mass death of epithelial and endothelial cells that express ACE2 receptor, which leads to increasing vascular permeability and causes aberrant production of anti-inflammatory cytokines and chemokines. Suppression of ACE2 leads to renin – angiotensin system dysfunction and additionally enhances the inflammation and vascular permeability.

— The overproduction of chemokines by epithelial cells facilitates the aberrant chemotaxis of monocytes, macrophages and neutrophils, which easily get into the focus of inflammation due to enhanced vascular permeability. It is also noteworthy that monocytes and macrophages express ACE2 and, hence, they are targets for SARS-CoV-2. The infected alveolar macrophages apparently become the key factor of COVID-19 pathogenesis and are responsible for the uncontrolled production of chemoattractants and inflammation mediators (cytokine storm).

— Apart from the renin – angiotensin system dysfunction, the uncontrolled systemic inflammatory response (cytokine storm), resulting from release of a large number of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1b, IL-6, IL-12, IL-13, IL-18, IL-33, TNF-α, TGFb, *etc.*) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, *etc.*) by the immune effector cells is the crucial factor for the development of ARDS and multiple organ failure, which are the main causes of COVID-19 lethality. In addition, the activated immune system cells in the focus of inflammation produce large amounts of reactive oxygen species, which cause further damage of the surrounding tissues and enhance the death of epithelial and endothelial cells.

— The death of epithelial and endothelial cells leads to a 'blood lake' in lung tissues and thrombin activation by tissue factors. In turn, activated thrombin cleaves fibrinogen to give fibrin, which cross-links into a polymer matrix (fibrin network) under the action of factor XIIIa formed from activated macrophages. The activated alveolar macrophages produce excess amounts of cytokines IL-5 and IL-13. Since high levels of IL-13 inhibit the expression of tissue plasminogen activator (tPA), lung tissue of COVID-19 patients has a reduced fibrinolytic ability and cannot cleave the resulting fibrin polymer matrix. As a consequence, the formation of the fibrin polymer matrix enhances the inflammatory response, increases the production of IL-5 and IL-13 and other Th2-cytokines. The formation and growth of the polymer fibrin matrix, accompanied by the infiltration of immune cells, forms the basis for the development of pulmonary fibrosis, one of the most serious complications of COVID-19.

— The increase in the vascular permeability, damage of epithelial and endothelial cells and high production of viral particles promote pronounced viraemia. The viral particles affect quite a few internal organs as well as immune cells and vascular endothelial cells. The damage of vascular endothelium induces vasculitis and thrombosis and, in severe cases, disseminated intravascular coagulation syndrome and even gangrene of extremities.

— The presence of viral particles in the systemic blood circulation disrupts recirculation of red blood cells, which is associated with the ability of viral particles to bind to the CD147 protein. In addition, SARS-CoV-2 causes a decrease in the haemoglobin concentration and haem dissociation to release iron and directly decreases the haem production. The decrease in the haem production weakens the repression of the aminolevulinic acid synthase (ALAS) gene and thus increases the production of haem precursors, which results in accumulation of intermediate toxic porphyrin metabolites. The accumulation of toxic porphyrin metabolites is likely to play a role in the development of neurovisceral symptoms of the disease such as headache, myalgia and fatigue, respiratory muscle paralysis and diarrhea.

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