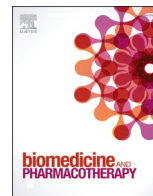




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Review

Molecular mechanisms involved in pathogenicity of SARS-CoV-2: Immune evasion and implications for therapeutic strategies

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the outbreak of unusual viral pneumonia that emerged in late 2019 in the city of Wuhan, China. Since then, because of its high transmission and pathogenic potential it spread almost all over the world causing the pandemic, as an extraordinary threat to the world public health. Rapid activation of a well-orchestrated and functional immune system with its both arms innate and adaptive immune response is pivotal to eradication of the disease caused by this coronavirus (COVID-19). Therefore, in this review are summarized the most recent data on complex molecular mechanisms involved in the innate and adaptive immune response to combat COVID-19. In addition to widely used vaccines against SARS-CoV-2, because of the induction of short-lived immunity and appearance of variants of concern (VOCs), there will be also discussed newly developed strategies to target different viral proteins, which are not prone to frequent mutations. Obviously, SARS-CoV-2 cannot evade the effect of these novel drugs and therefore they show a great promise as an antiviral therapy not only in COVID-19 but also in future viral outbreaks.

1. Introduction

In the last twenty-years, coronaviruses caused two epidemics, SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome). Since the outbreak of the mysterious pneumonia in Wuhan (Hubei province, China) in December 2019, in January 2020 a novel virus has been identified as the causative agent of a new life-threatening disease COVID-19 [1]. The International Committee of Virus Taxonomy classified this new virus as SARS-CoV-2 (Severe Acute Respiratory Syndrome coronavirus-2) based on standard practice, pathology, phylogeny and taxonomy [2]. SARS-CoV-2 is a zoonotic positive single-stranded RNA virus (+ve ssRNA) that belongs to Coronaviridae family and primarily affects birds e.g. bats [3], but has also the ability to cross species barrier from bats to humans [4]. It is further classified into the *Orthocoronavirinae* subfamily consisting of four genera: *alphacoronavirus*, *betacoronavirus*, *gammacoronavirus* and *deltacoronavirus*. While alphacoronaviruses and betacoronaviruses (SARS-CoV-2) infect exclusively mammalian species, gammacoronaviruses and deltacoronaviruses have a wider host range that includes avian species. Infections with human and animal coronavirus mainly result in respiratory and enteric diseases [5]. SARS-CoV-2 caused the third

ongoing pandemic that according to WHO as of 22 June 2022 resulted with more than 538.321.874 confirmed cases of COVID-19, including 6.320.599 deaths. On the other hand, as of 21 June 2022, a total of 11.912.594.538 vaccine doses have been administered (<https://covid19.who.int/>). The prerequisite for the development of effective treatments of COVID-19 is to understand the pathways of infection with SARS-CoV-2 as well as how our immune system responds to the virus by activating molecular mechanisms of innate and adaptive immunity.

1.1. Antigen structure and entry of SARS-CoV-2 in the host cells

SARS-CoV-2 is a novel positive-sense single-stranded RNA (+ssRNA, single linear RNA molecule) betacoronavirus with an average size of 60–120 nm diameter [6,7]. Similar to the other coronaviruses, SARS-CoV-2 encodes four structural components consisting of structural proteins S (spike), E (envelope), M (membrane) and N (nucleocapsid). The proteins S and M are responsible for the formation and stability of the viral envelope [8]. E protein (8–12 kDa) determines also the formation and composition of the viral membrane, whereas nucleocapsid protein enfold and protects the viral RNA [9].

All three surface proteins (S, M, E) are antigens, which may be used

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as targets for the development of potentially effective vaccines. SARS-CoV-2 spike protein as the most prominent protein consists of trimers (180–200 kDa) with a screw-like form including a larger head and a longer, thinner stalk. Morphologically, it forms a characteristic bulbous, crown-like (corona) halo surrounding the viral particle (Fig. 1) [10]. SARS-CoV-2 S-protein has a length of 1273 aminoacids and consists of S1 subunit, and the S2 subunit that are responsible for receptor binding and membrane fusion, respectively. The S1 subunit is composed of an N-terminal domain and a receptor-binding domain (RBD), the fusion peptide (FP), heptapeptide repeat sequence 1 (HR1), HR2, transmembraneTM domain, and cytoplasm domain [11]. Trimers of the SARS-CoV-2 S-proteins are coated with polysaccharide molecules [12], indicating that the virus is able to evade the host immune system by masking the spike glycoprotein (S protein) through extensive glycosylation. Thick coating of carbohydrate on highly immunogenic epitopes of the virus is a classic example of escaping from the surveillance of the host immune system [13]. SARS-CoV-2 glycosylation pattern is however different from other RNA viruses such as HIV in having greater concentration of N-glycan in comparison to O-glycans [14]. Glycan shielding is a critical feature of SARS-CoV-2 having great importance in the context of vaccine designing [15]. The insertion of a polybasic cleavage site for the proteolytic enzyme furin at the S1/S2 interface of spike protein is another remarkable feature of the SARS-CoV-2 genome, which is missing in all other SARS/SARS-CoV [16,17]. Furin, which is abundant in the respiratory tract, enables the cell–cell fusion without altering the viral entry into the cell and therefore increasing the virulence of SARS-CoV-2 [18].

1.2. Binding of the virus to ACE2 receptor

Coronaviruses enter the host cells and deposit their RNA into the host cytoplasm through endocytosis or direct membrane fusion. To enter host cells, SARS-CoV-2 recognizes the receptor angiotensin-converting enzyme 2 (ACE2) on host cells via the receptor binding domain (RBD) (Fig. 2A). Interestingly, this domain constantly switches between an “open” position for receptor binding and a “closed” position for immune evasion [19,20]. Moreover, structure analysis of SARS-CoV-2 RBD-hACE2 complex by crystallography revealed subtle but functionally important differences between SARS-CoV-2 and other SARS-CoVs in receptor recognition. Definitely, SARS-CoV-2 RBD possesses a

significantly higher hACE2 binding affinity than RBD of other SARS-CoVs [21]. Residues from 318 to 510 in the S1 region are enough for high-affinity binding to the peptidase domain of ACE2 [22]. The cryo-electron microscopy have demonstrated that the binding affinity of SARS-CoV-2 S-protein to ACE2 is approximately 10–20 times greater than that of S protein of other SARS-CoVs [22,23].

The second step of the viral entry is cleavage between the S1 and S2 subunits of the viral glycoprotein which is regulated either by the receptor transmembrane protease serine 2 (TMPRSS2) (Fig. 2B) that is a member of the Hepsin/TMPRSS subfamily or by endosomal cysteine proteases cathepsins B and L [24,25]. Both heptapeptide repeat 1 (HR1) and heptapeptide repeat 2 (HR2) regions of the S2 subunit of S protein interact after cleavage interact to form the 6-helix bundle (6HB) fusion core [26,27] as a critical step in facilitating and completion of the fusion of viral membrane with the host cell membrane. Fusion process is a prerequisite for viral internalization, intracellular release of the viral content, replication, and subsequent infection of other cells (Fig. 2). Once within the cell, endosomal acidification induces virus-endosome membrane fusion, thereby leading to viral uncoating (viral RNA release) for the initiation of viral replication and infection [28]. ORF-1a and ORF-1b translation results in the formation of two large poly-proteins (pp1a and pp1ab), which are then cleaved by three functional proteases into 16 non-structural proteins (NSP 1–16). These non-structural proteins are important in giving rise to the viral RNA polymerase and other accessory proteins for virus assembly [29,30]. Combination of the +ve ssRNA with capsid protein forms the nucleocapsid that may be followed by budding of assembled virus particles in endoplasmic reticulum and Golgi body [31]. These newly generated virions fuse lastly with the cell membrane for effective shedding of the virus in the neighboring healthy cells [32]. Highly contagious SARS-CoV-2 virions released into the surrounding environment via respiratory droplets may attack the cells expressing high levels of ACE2 receptor e.g. airway and alveolar epithelial cells, the vascular endothelial cells and lung macrophages, as well as brain, cardiac, gastrointestinal and renal tissues [33].

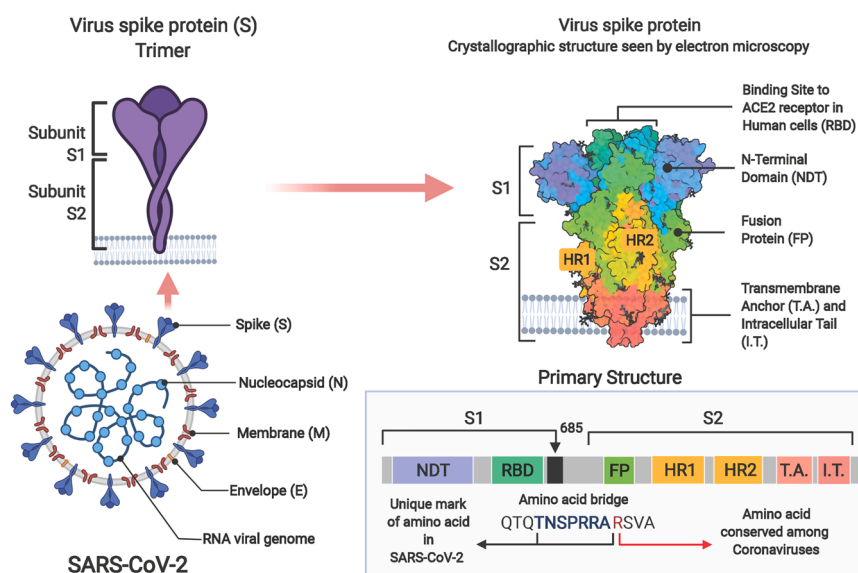


Fig. 1. Structure of SARS-CoV-2. Diagram showing the single stranded RNA genome and proteins present in coronavirus as well as primary and 3D-structure of spike protein.

Adapted from “An in-depth look into the structure of the SARS-CoV-2 spike glycoprotein” by Biorender.com.

SARS-CoV-2 Entry through Host ACE2

Intracellular replication cycle of SARS-CoV-2

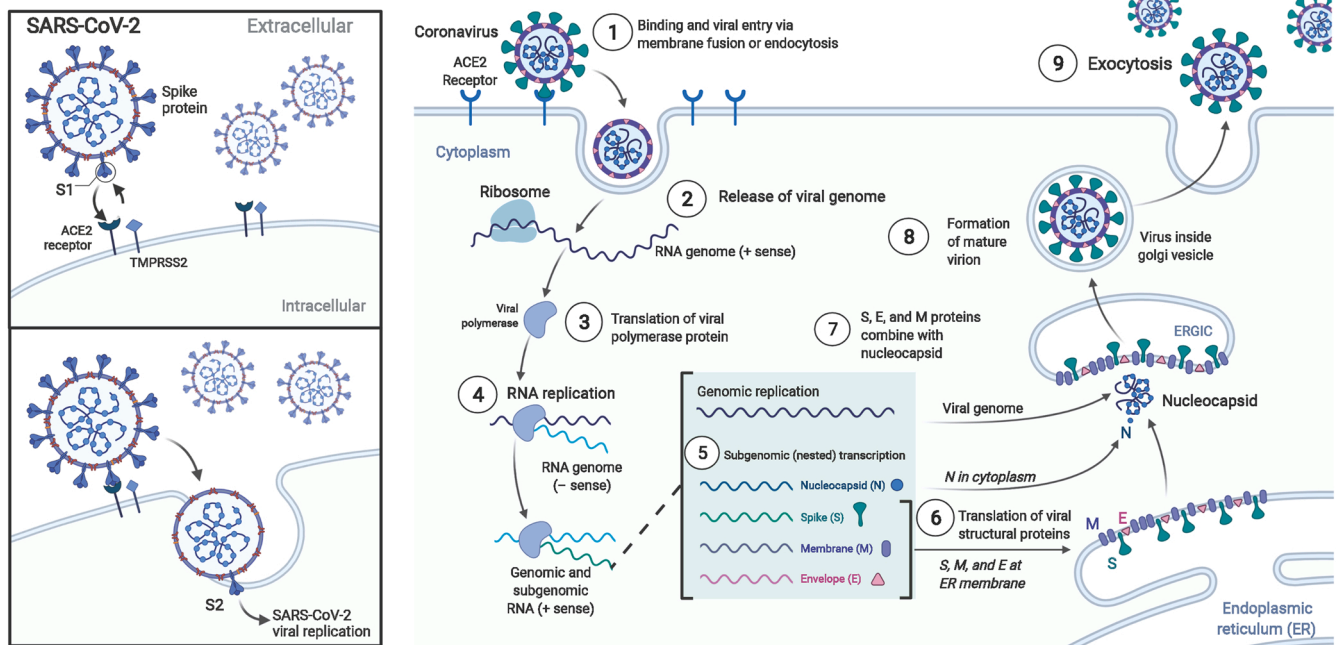


Fig. 2. Cell entry and intracellular replication cycle of SARS-CoV-2. On the left side is presented SARS-CoV-2 cell entry through host ACE2, while on the right side is presented intracellular life cycle of SARS-CoV-2 in 8 steps, starting from the release of viral genome (step 2) till generation of mature virions (step 8) and their exocytosis (step 9).

Adapted from "Corona replication cycle" by Biorender.com.

2. Innate and adaptive immunity to SARS-CoV-2

2.1. Innate immunity

Once within the target cells SARS-CoV-2 elicits the host innate and adaptive immune response, i.e. it triggers generation of both specific neutralizing antibodies and antiviral-specific immune cells. Pattern recognition receptors (PRRs), as one of the important components of the innate immunity, play a key role in detection of viral infection and activation of inflammatory pathways that finally promote viral clearance. They can be located on the membrane, in the cytosol, and in the nucleus. PRRs are responsible for recognizing unique molecular patterns from pathogens known as pathogen-associated molecular patterns (PAMPs) and endogenous molecules released from damaged and dying cells known as damage-associated molecular patterns (DAMPs). There are many more different PRRs, but the most important are five primary PRR families, including Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), C-type lectin receptors and absent in melanoma 2 (AIM2) receptors [34]. It has been shown, however, that only several PRRs in particular TLRs, RLRs, NLRs and inflammasome activate their signaling pathways in response to SARS-CoV-2. Activation of the innate immunity at the onset of infection with this virus is initiated via recognition of viral single-stranded RNA (ssRNA) and double stranded RNA (dsRNA) as PAMPs. For this recognition are responsible PRRs present in the cytosol of immune cells such as retinoic acid-induced gene 1 (RIG-I)-like receptors (RLRs) [35]. In addition to RLRs, toll-like receptors (TLRs, mainly TLR 3, 7, and 8) present in endosomes are the first to identify the virus and lead to enhanced interferon (IFNs) production, as the most important for the antiviral defense [36]. Type I/III interferons together with other cytokines which are secreted as a result of downstream signaling cascade upon PRR activation, such as proinflammatory tumor necrosis factor alpha (TNF- α), and interleukin-1 (IL-1), IL-6, and IL-18 induce antiviral

programs in target cells and potentiate the adaptive immune response. The cells of innate immunity (monocytes, macrophages, neutrophils and dendritic cells-DCs) secrete a series of proinflammatory cytokines and are armed with an arsenal of PRRs that recognize PAMPs and home to the site of infection [37,38]. This recognition may also stimulate the innate lymphoid cells such as natural killer (NK) cells that are responsible for directly killing virus-infected cells through degranulation and receptor mediated apoptosis [39]. Dysregulated function of the first line defense cells (monocytes, macrophages, neutrophils, NK cells, and DCs) plays a key role in the development of hyperinflammation state observed in COVID-19 patients with severe disease known as a cytokine release syndrome (CRS) [40]. Especially, the overactivation of ACE-2 expressing lung macrophages results in the overproduction of IL-6 [41], which in complex with the macrophage activation syndrome deteriorates the recovery of COVID-19 patients [42]. Some immunological hallmarks may be predictive to progression and the outcome of the disease. The most characteristic findings in severe forms of COVID-19 are elevated neutrophil: lymphocyte ratio [43], significant decrease of NK cells [39] and an upregulation of NKG2A in COVID-19 patients with the exhaustion of cytotoxic T cells and NK cells at the early stage of SARS-CoV-2 infection [44]. IFN-I can effectively limit infection with corona viruses [45,46], whereby SARS-CoV-2 seems to be more sensitive to the pre-treatment with IFN-I/III in vitro than SARS-CoV-1 [47,48]. Therefore, secretion of the IFNs plays a key role for the activation of interferon-induced genes (ISGs) which interfere with the spike protein mediated membrane fusion of SARS-CoV-2 [49] and interferon-induced transmembrane family of proteins (IFITMs) providing the intrinsic defense against virus entry into cells [50]. The most important of these proteins is IFITM3, which is found in lysosomes and endosomes and can effectively inhibit SARS-CoV-2 proliferation and invasion by preventing its release into cytoplasm [50]. As one of the reasons for the severity of COVID-19 with the development of cytokine release syndrome may be the fact that circulatory and lung immune cells express less IFITM3 than other organs [51]. SARS-CoV-2 infection activates also NOD-like

receptors (NLRs) by inducing production of type I of IFNs and pro-inflammatory cytokines [52]. In addition to NLRs, SARS-CoV-2 PAMPs triggers inflammasome sensors in particular NLRP3. This results in activation of caspase-1, production and release of IL-1 β and IL-18 and cleavage of gasdermin D inducing the pyroptotic cell death [53]. Another viral detection sensor within the cell is the cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) signaling pathway. It is usually activated upon detection of cytoplasmic DNA, which is released from damaged mitochondria after infection with SARS-CoV-2 [54]. This is a critical mechanism for limiting the replication of both DNA and RNA viruses after cell infection [55,56].

2.2. Adaptive immunity

Once the body's first line of defense (innate immunity) to SARS-Cov2 fails, the second arm of the immunity is activated to effectively eradicate infected cells with this virus.

This process occurs a few days after viral exposure and viral detection, which triggers the activation of various transcription factors and therefore promoting secretion of pro-inflammatory chemokines and cytokines tumor necrosis factor alpha (TNF- α), interleukin (IL)–1 and IL-6, amongst others [40]. On the other hand, type I IFN response induces maturation of dendritic cells, monocytes and macrophages into antigen presenting cells (APCs). These cells, in turn, present viral antigenic peptides of structural (S, M, N, E) and multiple non-structural proteins [57] in complex with the class II of major histocompatibility complex (HLA-Class II) [58,59]. Presentation of these antigens on APCs via binding on T-cell receptor (TCR) activates differentiation of CD4 + and CD8 + T lymphocytes as well as regulatory T-cells (T-regs) [58,59]. CD4 + follicular helper cells influences naïve B-lymphocytes to proliferate and undergo somatic hypermutation. This increases their antibody affinity within lymphoid microenvironment known as germinal centers [60,61]. Epitopes of structural proteins S and N elicit immunoglobulin production, with IgM being produced as the first immunoglobulin [62]. At the onset of infection, the B cell response is directed against N protein. Even though it is a smaller than S protein, it is highly immunogenic due to absence of glycosylation sites [63]. Antibodies directed to the region-binding domain of the S protein may be detected 4–8 days after the appearance of initial symptoms [64], all of them (IgM, IgA and IgG) show a neutralizing activity [65]. While IgM levels started to decline after 3 months the level of IgG was detected for a longer period, [66]. Immunoglobulin A is predominantly secreted by mucosa-associated lymphoid tissue (MALT) of the respiratory system and plays a crucial role in prevention of virus binding to the mucosal epithelium [67] and its deficiency may exacerbate COVID-19 infection [68]. Therefore, it is a major effector molecule to defend the physical barriers against viruses. Specific IgA response to the infection with virus is stronger and more persistent than IgM response being detectable within the first week in 75% of the patients [69,70]. In contrast to IgM and IgA antibodies, which are detected 5 days after the onset of symptoms IgG was detected after 14 days and last for longer. It seems that the intensity of the IgG response is related to both viral load and COVID-19 severity [71]. In line with this, Long et al. [72] found in asymptomatic individuals significantly lower levels of SARS-CoV-2 IgG than in patients with severe form of disease. In contrast to asymptomatic individuals, plasmablasts of the patients with severe COVID-19 display an oligoclonal expansion [73], a reduced expression of genes involved in glycolysis [74] and an upregulation of apoptosis-related genes [75]. Recent observations support the hypothesis that the innate immunity is crucial to viral infection [76], and that neutralizing antibodies do not play a critical in the immune response to SARS-CoV-2. This is best illustrated from two small series of COVID-2 patients with primary humoral immunodeficiencies (agammaglobulinemia), who despite developing pneumonia displayed a more favorable outcome than patients with common variable immunodeficiency [77,78]. This may be due to disability of patient with agammaglobulinemia to generate antibodies

against SARS-CoV-2, but they maintained an intact innate immunity or acquired cellular immune response. In addition to the viral antigens, neutralizing antibodies also interact with natural killer cells through Fc-receptor (CD16). This triggers the antibody-dependent cell-mediated cytotoxicity (ADCC) response, important in killing of infected cells with the virus [39].

Due to downregulation of MHC class I and II molecules SARS-CoV-2, similarly to other coronaviruses, is capable of inhibiting the T- cell mediated immune responses by restraining antigen presentation [44]. In mild forms of disease, the lymphocyte count of both T cells (CD3 +) and CD8 + T cells (CD3 +CD8 +) was found to be significantly higher than in patients with severe disease. However, in both mild and severe forms of COVID-19, the number of CD8 + T cells was decreased compared to healthy donors [79]. Phenotypic analysis demonstrated that CD8 + T-cells express high levels of CD57, which further suggests the increased senescence of these cells in COVID-19 [80]. Despite decreased number of T cells, both CD4 + and CD8 + T cells expressed increased levels of activation markers e.g. HLA-DR, CD38 and the Ki-67, a marker of T cell proliferation. These parameters correlated with the severity of the disease [73]. In addition, CD8 + T cells in COVID-19 patients were found to less degranulate (decreased CD107a externalization) and consequently produced less IL-2, IFN γ , and granzyme B than healthy controls [44]. Moreover, T cells (CD4 + and CD8 +) of bronchoalveolar lavage (BAL) from COVID-19 patients expressed more increased levels of PD1 than T- cells in peripheral blood [81]. Compared to T cells in patients with mild disease or healthy donors, T cells of patients from intensive care units (ICUs), expressed significantly higher levels of PD-1. [82]. Noteworthy, CD8 + T cells were present in a decreased number in BAL of severe patients than in patients with moderate infection, suggesting their important role in SARS-CoV-2 eradication [83].

Analogous to long-lived plasma cells, which have the potential to produce antibodies for decades, generation of specific T- cells with memory plays a key role for durable protective immunity against SARS-CoV-2. Despite the heterogeneity between donors, it has been estimated that the magnitude of the SARS-CoV-2-specific CD4 + and CD8 + memory T cell response is typically around 0.5% and 0.2% of the repertoire [84] and targets at least 19 and 17 epitopes, respectively [57]. All these studies demonstrate that SARS-CoV-2 possess a great potential to effectively suppress the adaptive immune responses.

3. Evasion mechanisms of SARS-CoV-2

As mentioned previously, the first step in establishing the antiviral response is activation of the innate immunity by recognizing of viral single-stranded RNA (ssRNA) and double stranded RNA (dsRNA) as pathogen-associated molecular patterns (PAMPs) via pathogen recognition receptors (PRRs). PRRs are present in the cytosol of immune cells such as retinoic acid-induced gene 1 (RIG-I)- like receptors (RLRs) [35] and endosomal toll-like receptors (TLRs). These are mainly toll-like receptors 3, 7, and 8, which are the first to identify the virus and lead to enhanced interferon (IFNs) production, as the most important for the antiviral defense [36]. One of the key transcription factors, which is largely responsible for the development of the antiviral state in infected cells, is interferon regulatory factor 3 (IRF3). It belongs to IRF family consisting of nine members in mammalian cells [85], which display various cell functions including innate immunity, cell cycle progression, apoptosis and tumor suppression [86,87]. Among them, IRF3 and IRF7 are key regulators of the innate antiviral immunity by inducing production of type-I interferons (e.g. IFN β) [88]. The secreted IFN β binds to its receptor IFNAR (IFN- α/β receptor) expressed on the surface of the infected or yet uninfected cells [89,90]. On the other hand, IFN signaling via JAK/STAT pathway activates ISGF3, which in turn induces IFN-stimulated genes (ISGs). These molecules help establish an antiviral state in the infected cell by inhibiting specific stages of the virus replication [91]. Noteworthy, many ISGs can be induced directly by IRF3, without the requirement of IFN signaling [92]. In addition to its

transcriptional function, IRF3 is also activated to trigger apoptosis of virus-infected cells, as an antiviral mechanism to restrict virus spread within the host. This is called RIG-I-like receptor-induced IRF3 mediated pathway of apoptosis (RIPA). Both these functions of IRF3 work in concert to induce a protective immunity against infection with viruses [93] (Fig. 3).

DMV: double membrane vesicle; TRIM25: Tripartite Motif Containing 25, it is an E3 ubiquitin/ISG15 ligase; Traf6 complex: TNF receptor-associated factor, it is an ubiquitin E3 ligase; MAVS: Mitochondrial antiviral-signaling protein, is an essential protein for antiviral innate immunity. Adapted from "Innate immune antagonism by SARS-CoV-2" by Biorender.com.

3.1. Evasion of native immune response by means of structural viral proteins

SARS-CoV-2 as all coronaviruses produce the main structural proteins envelope (E), membrane (M), spike (S) and nucleocapsid (N) [94]. M-protein is the most abundant structural protein, which interacts with all other structural proteins of coronaviruses and antagonizes IRF3 in different ways e.g. by inhibiting of its downstream phosphorylation. It inhibits production of type I and III interferon production by targeting RIG-I/MDA-5 [95]. On the other hand, structural protein N (nucleocapsid) inhibits IRF3 activation and consequently type-I IFN production in the early PRR recognition stage of the signaling pathways [96] and also through suppression of RIG-I ubiquitination and activation [52].

3.2. Evasion of immune response by means of non-structural and accessory viral proteins

SARS-CoV-2 utilizes various proteins to antagonize IRF3 activation as an antiviral pivotal defense mechanism. Papain-like protease (PLpro) is an important enzyme, which processes viral polyproteins and promotes its spread. PLpro domain of non-structural protein-3 (NSP3) through direct interaction prevents phosphorylation and nuclear translocation of IRF3 [97]. SARS-CoV-2 non-structural protein 1 (NSP1) suppresses virus-dependent IRF3 phosphorylation and dimerization [98]. SARS-Cov-2 circumvents the recognition of its short double-stranded RNA by RIG-I, whereas recognition of long dsRNA by MDA-5 (melanoma differentiation-associated gene 5) by adding a /-methylguanylate cap in the blunt 5' end of viral RNA. This evasion process is carried out by non-structural proteins NSP13, NSP14 and

NSP16, which are highly conserved in the group of betacoronaviruses [99,100]. Detection of viral RNA by MDA-5 can be also evaded by NSP15, which shortens and prevents the accumulation of 5'-poly-U-containing, negative-sense coronavirus RNA [101]. Experimental data support the evidence that SARS-CoV-2 NSP15 binds to the E3 ubiquitin ligase Nrdp1, which "preferentially" promotes TLR-mediated production of type I interferon, resulting in a decrease of IFN β -reporter activity [102,103]. Even though the accessory viral proteins possess activities, which are not essential to viral replication, they may play a role in pathogenesis of COVID-19. Among nine accessory proteins identified in SARS-CoV-2 only some of them are able to antagonize IRF3 e.g. SARS-CoV-2 Orf6 shows attenuative effects on IRF3-induced IFN- β -promoter activation via the C-terminus, which is critical for its antagonistic activity [104]. In addition, SARS-CoV-2 can antagonize cGAS-STING signaling via its accessory proteins ORF3a and 3CLcan, resulting in suppression of the antiviral immune response [105].

3.3. Dysregulated release of type I IFN: cytokine release syndrome- CRS

Recognition of SARS-CoV-2 by PRRs induces concurrent release of both IFNs and other pro-inflammatory cytokines including IL-1 β , TNF, IL-6, IL-12, IL-17 and others [38]. Type I IFN release represents the major mechanism in both limiting SARS-CoV-2 replication [106] and the development of the adaptive immune response (maturation of APCs, activation of NK cells, CD4 + and CD8 + T cells) [107]. Therefore, dysregulation of type I IFN response profoundly affects the establishment of both effective innate and adaptive immune response against SARS-CoV-2. Excessive immune response to SARS-CoV-2 infection is known as cytokine storm or cytokine release syndrome (CRS), which is characterized by the hyperactivation of immune cells and excessive production of inflammatory cytokines and chemical mediators [108, 109]. High levels of circulating cytokines, severe lymphopenia, thrombosis and massive mononuclear cell infiltration of multiple organs appears to be the main cause of disease severity and death in patients with COVID-19 [110,111]. The severity of COVID-19 depends on impaired type I IFN response, with no IFN- β and low IFN- α production [112,113]. Accordingly, a genetic study has shown that loss of function variants affecting type I IFN response are significantly enriched in patients with severe life-threatening SARS-CoV-2 pneumonia [114]. The presence of neutralizing autoantibodies against type I IFN contributes to the development of severe COVID-19 [115], indicating that viral-mediated delayed production of type I IFN is the first step towards COVID-19 worsening.

Therefore, patients with severe forms of COVID-19 exhibit higher levels of inflammatory cytokines (IL-6, TNF- α , IL-2, IP-10, MCP-1, macrophage inflammatory protein 1 alpha, and granulocyte-CSF) than patients with mild and moderate form of disease [43,116]. IL-6 circulating levels are significantly higher in severe than mild to moderate forms of disease, predicting the severity of disease and its outcome [117]. Inflammatory markers (C-reactive protein, serum amyloid A, ferritin, fibrinogen) are also highly increased and correspond also to elevated levels of serum cytokines and many chemokines (CCL2, CCL7, CCL8 etc.) [118]. These proinflammatory cytokines have pleiotropic effect including activation of coagulation that is followed by elevated levels of D-dimer as a biomarker of COVID-19-associated coagulopathy [119]. In severe forms of COVID-19, a sustained decrease of lymphocyte counts of T cells (especially CD8 + cells) and an increased neutrophil-to-lymphocyte ratio (NLR) was observed, which might be predictive of COVID-19 outcome [43]. The presence of SARS-CoV-2 virus particles in bronchial and alveolar type II epithelial cells induced pathological alterations including pulmonary edema, diffuse alveolar injury with the formation of hyaline membranes, proteinaceous aggregates, fibrinous exudates, monocytes and macrophages within alveolar spaces, and inflammatory infiltration of interstitial mononuclear cells [120,121]. On the other hand, immunohistochemical analysis showed

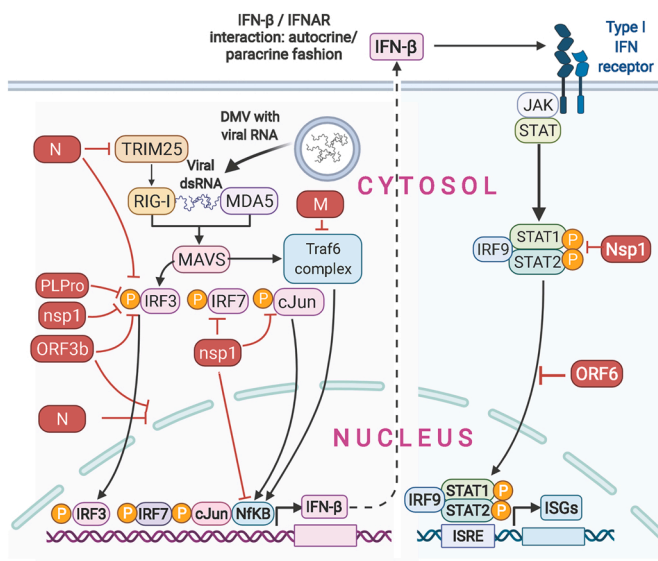


Fig. 3. Evasion mechanisms of SARS-CoV-2 from the innate immune response.

and more CD8 + T cells than CD4 + cells within the alveolar septa [122, 123].

4. Discussion

4.1. The long-standing conundrum: why some patients are asymptomatic and others develop severe form of COVID-19?

Clinically, COVID-19 can be categorized as mild, moderate, severe and critical. It could be manifested with fever, dry cough, sore throat, shortness of breath, tiredness, acute respiratory distress syndrome (ARDS) and pneumonia with varying degree of severity [124,125]. However, the conundrum why some individuals develop a mild to asymptomatic form of COVID-19, compared to persons who develop a severe form of disease remains to be elucidated. The best way to address this issue is to study molecular mechanisms protecting the children/younger age groups against SARS-CoV-2 infection.

4.1.1. Pattern recognizing receptors (PRR)

To understand the higher capacity of children for controlling SARS-CoV-2 infection at an early stage Loske et al. [126] in a recent study analyzed the single-cell transcriptomics of the upper airways of children with mild COVID-19. Higher basal expression of relevant PRRs such as MDA5 and RIG-I in upper airway epithelial cells, macrophages and dendritic cell of children resulted in a stronger innate antiviral response than in adults. In addition, in children were detected predominantly distinct immune cell subpopulations including *KLRC1* (NKG2A)⁺ cytotoxic T cells and a CD8⁺ T cell population with a memory phenotype. This study provided evidence that the airway immune cells of children are primed for virus sensing, resulting in a stronger early innate antiviral response to SARS-CoV-2 infection than in adults. Several other studies [113,127,128] corroborated the evidence that severe COVID-19 in adults may be linked to an impaired antiviral response in the nasal epithelium and blood.

Recently, Yoshida et al. [129] in a very comprehensive study uncovered multiple mechanisms, which again explain the phenomenon why children are generally protected from severe COVID-19. First, they showed that the airway epithelium has a higher steady-state expression of IFN-response genes in children and as SARS-CoV-2 is highly sensitive to prestimulation with interferons, this preactivation may restrict viral spread in children. Second, the systemic immune response in blood is characterized by a more naive state, in contrast to adults who display a highly cytotoxic immune compartment in the blood, probably due to a failure to restrict viral spreading. A third feature that they observed was the higher TCR repertoire diversity in children versus adults and finally they found previously undescribed IFN-stimulated states in multiple blood cell lineages that are highly abundant in early disease in adults.

Children not only have a different innate immunity, but they also develop a different humoral arm of the adaptive immunity i.e. antibody response to SARS-CoV-2 infection. Weisberg et al. [130] showed recently distinct antibody responses in children and adults after SARS-CoV-2 infection. Children with and without multisystem inflammatory syndrome (MIS-C) had reduced spectrum of anti-SARS-CoV-2-specific antibodies, predominantly generating IgG antibodies specific for the S protein but not the N protein. In contrast, adult COVID-19 cohorts had anti-spike (S) IgG, IgM and IgA antibodies, as well as anti-nucleocapsid (N) IgG antibody. Compared to adult COVID-19 cohorts, children displayed reduced neutralizing activity, suggesting a reduced protective serological response.

4.1.2. ACE-2 and TMPRSS2 expression

In addition to these differences, many reports indicate that other host factors may play also a decisive role to the clinical course and outcome of COVID-19. As ACE2 receptors are the main entry site of SARS-CoV-2, it was postulated that the severity of COVID-19 in children might be related to the lower expression of these receptors in the upper and lower

airways compared to the highest expression found in nasal epithelium of healthy adults [131–133]. In turn, over-regulation of ACE2 may give rise to more receptors for virus entry, which leads to a higher viral load with unfavorable prognosis [134]. Accordingly, blocking of S protein binding sites with human recombinant soluble ACE2 induces an inhibition of SARS-CoV-2 in engineered human tissues [135] and a decrease of coronavirus load by a factor 1000–5000 in a clinical study [136].

In addition to ACE2, TMPRSS2 as a second host protein implicated in the infection of cells with SARS-CoV-2 may also affect the susceptibility of patients for COVID-19. It was demonstrated that an intergenic single nucleotide polymorphism (SNP) which is associated with the increased expression of TMPRSS2 and decreased interferon inducible gene expression in lung tissue increased the susceptibility of individuals who carry this type of SNP to COVID-19 [137].

Recently, it has been reported that some genetic systems may play an important role in the predisposition of individuals for SARS-CoV-2 infection. Several alleles of class I or class II HLA antigens may be correlated with COVID-19 occurrence e.g. Nguyen et al. [138] predicted the binding affinity of SARS-CoV-2–145 HLA class I alleles, and the top presenters of conserved peptides were found to be HLA-A* 02:02, HLA-B* 15:03, and HLA-C* 12:03. On the other hand, the unusual pattern of immune dysregulation in extreme COVID-19 was characterized by low HLA-DR expression regulated by IL-6 and lymphopenia, combined with prolonged development of cytokines and hyper-inflammation [139].

Even though the impact of ABO blood groups on COVID-19 outcomes remains elusive, there are some reports, which demonstrate this correlation. One study reported that blood group O correlated with reduced risk for the disease [140]. Another group demonstrated that antibodies against human A antigen might inhibit the binding between SARS-CoV and its receptor. This could be a reason why people with blood type O are less likely to get the virus [141]. However, there may be also other mechanisms, which should be further elucidated.

4.1.3. Opsonizing antibodies that facilitate entry of SARS-CoV-2 in ACE2 negative cells

Very recently, two study groups [142,143] independently observed that in patients with severe forms of COVID-19 the virus could infect and replicate in macrophages of human lungs. Because macrophages do engulf infected cells with the virus, they were not sure, whether intracellular viruses do originate from these cells or they directly infect these cells. However, they were puzzled by the fact, how could macrophages be infected when they do not carry many or no ACE2 receptors. The authors showed that when the antibody-opsonized virus encounters Fcγ receptors of monocytes, instead of being disabled, it sneaks into these cells. After infection of cells with SARS-CoV-2, human macrophages activate inflammasomes, release IL-1 and IL-18 and undergo pyroptosis. It induces the hyperinflammatory state of the lungs [143]. Lieberman et al. [142] claims that not all but only monocytes with Fcγ receptor could be infected, and not all antibodies facilitates viral entry e.g. antibodies generated after vaccination with Pfizer-BioNTech did not allow monocytes to take up SARS-CoV-2. The type of antibodies that facilitate viral intake from monocytes, remains still to be elucidated.

5. Strategies how to outsmart SARS-CoV-2

The evasion strategies of SARS-CoV-2 can be harnessed in the development of novel therapeutic drugs for the treatment of ongoing and future pandemic. Moreover, because of the reduced efficacy of widespread vaccination due to newly emerging variants of concern (VOCs), there is an urgent need for the development of novel host-directed effective antiviral drugs [144,145].

Thus far, three antivirals have been approved for clinical use against SARS-CoV-2. Remdesivir is a direct-acting antiviral targeting the viral RNA-dependent RNA polymerase that catalyzes the synthesis of viral RNA [146]. In contrast to Remdesivir that is administered intravenously

[147], PF-07321332 (paxlovid) and MK-4482/EIDD-2801 (molnupiravir), have also been developed as oral clinical candidates. Paxlovid targets the coronavirus's main protease (3CLpro, also called Mpro), an essential protease involved in processing viral replicase polyproteins while molnupiravir is a ribonucleoside analog that inhibits viral replication [148,149]. In addition, Unoh et al. [150] reported the first oral noncovalent, nonpeptidic SARS-CoV-2 3CL protease inhibitor clinical candidate S-217622, which was very effective both in vitro and in vivo by inhibiting intrapulmonary replication of SARS-CoV-2 in mice.

In contrast to direct-acting antivirals, development of small molecules directed against host factors, which are not prone to mutations like viral VOCs, would be another strategy to effectively combat COVID-19. As previously stated, the most attractive pharmacological targets to impede viral entry include ACE2 and TMPRSS2 receptor. It has been reported that the employment of the soluble form of ACE2 could be a rational treatment approach because the injection of ACE2 can both competitively neutralize the virus and ameliorate lung damage [121, 151]. In addition, the use of clinical-grade ACE2 recombinant human solution (hrsACE2) can prevent SARS-CoV-2 from entering host cells and reduce viral load in a dose-dependent manner. However, it seems that the use of hrsACE2 is useful only in the early stages of the disease and prevents viral infection of human blood vessels and renal organoids [136]. Despite several ACE2 and ACE-2 like molecules being developed for treatment of COVID-19, Tsai et al. [152] developed an ACE2-Fc fusion protein, SI-F019, which showed a strong binding and a more potent neutralization of SARS-CoV-2 variants compared to the original strain. These findings suggested that SARS-CoV-2 cannot evolve to escape the ACE2-Fc inhibitor, in contrast to monoclonal antibodies binding to spike, which can be clearly evaded by viral escape variants. In addition, Shapira et al. [153] identified and characterized a small-molecule compound, N-0385, as a novel effective early treatment option against COVID-19 and emerging SARS-CoV-2 variants of concern. It exhibits potency and a selectivity index of $> 10^6$ at inhibiting SARS-CoV-2 infection of human lung cells in low nanomolar concentrations.

Aptamers are single-stranded DNA or RNA oligonucleotides (20–80 nucleotides). Because of their high specificity, sensitivity and binding affinity to the target molecules appear to be a versatile diagnostic and therapeutic tool for different viral proteins of SARS-CoV-2 and especially in detecting its new variants [154,155]. One of the best examples for an aptamer is BC 007, which demonstrated specific binding to two crucial growth proteins of the SARS-CoV-2 virus, the spike protein and the RNA-dependent RNA polymerase. Because of its neutralization potential of cross-reactive autoantibodies in COVID-19, this aptamer could also provide future therapeutic options for treating patients suffering from autoimmune-associated post-COVID-19 symptoms [156].

In addition, the use of CRISPR-Cas13d to target highly conserved sequences of the SARS-CoV-2 genomes was proven to be capable of cleaving SARS-CoV-2 fragments in human lung epithelial cells [157]. In order to improve the delivery efficiency the CRISPR-Cas13 machinery into the airway epithelium it can be performed with the use of a modified adeno-associated virus (AAV), i.e. a non-pathogenic human virus with an affinity for the airway epithelial cells [158].

6. Conclusion and future perspective

An early-established and well-orchestrated function of innate and adaptive immune system contributes to a rapid eradication of infection with SARS-CoV-2. In contrast, dysregulation of both arms of immunity induces a worsening of COVID-19 that affects many vital organs, in particular the lungs. Identification of complex molecular mechanisms involved in the pathogenicity of SARS-CoV-2 will help designing of future appropriate therapeutics. In addition, because of the short-lived immunity induced by application of vaccines against SARS-CoV-2 and due to appearance of new virus mutations or variants of concern (VOCs), researcher worldwide are developing novel strategies to target viral

proteins, which are not prone to frequent mutations.

Despite extensive investigations, some unmet needs are still to be addressed in the future in order to overcome challenges that may hinder drug development for COVID-19.

- More research on the interaction between SARS-CoV-2 and host cells, which may reveal new signaling pathways. Changes in the signaling pathways caused by the infection may also contribute to the elucidation of the molecular cascades that trigger infection and the severity of the clinical symptoms.
- More research of numerous components of the innate and adaptive immune response, ranging from serum proteins, antigen presentation, and cytokine response to COVID-19 clinical progression.
- Given the evidence that the severity of COVID-19 may also be linked to multiple genetic factors, the investigation of blood groups, HLA-system and SNP profiles of the ACE2 and TMPRSS2 genes would contribute in identification of population at risk i.e. in creating a risk score for SARS-CoV-2 infection.
- More research should be done on novel agents such as aptamers, which could be delivered intranasally, as well as anti-TNF-agents and agents targeting neutrophilia and monocyte dysfunction in COVID-19.
- Identification of immunological biomarkers and machine learning, which may be used to identify the highest priority patients for COVID-19 treatment.
- In addition to this research, attempts should be done in defining a well-balanced diet (e.g. combination of healthy food rich in vitamins and minerals and hydration) to boost the immune system, which could prevent development of COVID-19 or at least mitigate its clinical course [159].
- Although many challenges have to be overcome before their clinical application, these novel drugs should be tailored according to the stage of COVID-19, and to an in-depth understanding of SARS-CoV-2 pathogenesis. Once established, these drugs will be a great promise as an antiviral therapy not only for the treatment of COVID-19 but also for future viral outbreaks.

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