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IL-6: Relevance for immunopathology of SARS-CoV-2

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ABSTRACT

COVID-19 mortality is strongly associated with the development of severe pneumonia and acute respiratory distress syndrome with the worst outcome resulting in cytokine release syndrome and multiorgan failure. It is becoming critically important to identify at the early stage of the infection those patients who are prone to develop the most adverse effects. Elevated systemic interleukin-6 levels in patients with COVID-19 are considered as a relevant parameter in predicting most severe course of disease and the need for intensive care. This review discusses the mechanisms by which IL-6 may possibly contribute to disease exacerbation and the potential of therapeutic approaches based on anti-IL-6 biologics.

1. Introduction

At the end of 2019 and the beginning of 2020, first, China and then the rest of the world have been confronted with an outbreak of a new airborne transmitted coronavirus disease 2019 (COVID-19), a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Just a few months later, there are already millions infected worldwide and with borders closed and strict travel bans imposed local transmission patterns are in place in most countries [1]. COVID-19 mortality rate appears to be in the range of 3,4–5,5% [2], which is significantly higher than that for seasonal flu caused by the influenza virus (1%), but lower than for both severe acute respiratory syndrome (SARS) (15 %) [3] and Middle East respiratory syndrome (MERS) (34 %) [4]. At the same time, the COVID-19 transmission rate is much greater than those of MERS or SARS, and poses a real threat to life for a large number of people worldwide, especially, in older patients with other co-morbidities [5]. Thus, in the absence of effective vaccines and treatments, early detection and the ability to define prognostic parameters predicting the course of the disease appear to be of particular interest.

2. COVID-19 pathogenesis and IL-6

Coronaviruses represent a large family of zoonotic respiratory viruses [6] that can cause both seasonal cold symptoms and fatal respiratory failure associated with severe inflammation of lower respiratory tract [7]. The major clinical symptoms of COVID-19 are similar to those experienced during a seasonal flu infection and include fever, dry cough, headache, myalgia and others. Co-morbidities such as cardiovascular diseases, diabetes, respiratory diseases, hypertension and age may exacerbate the disease manifestations [8,9]. Both moderate and severe COVID-19 infections cases may result in pneumonia with fluffy opacities on the chest computer tomographic scans, lung edema and accumulation of pleural fluid in the lungs [10,11]. Severe cases require invasive oxygen supply.

The exact molecular mechanisms of COVID-19-mediated pathogenesis are still under investigation. However, the lessons learned from SARS-CoV and MERS-CoV infections may uncover some key features of COVID-19-related pathologies, as well as molecular mediators and signaling pathways involved. The genetic sequence of SARS-CoV-2 [12], which was released almost simultaneously with the first reported cases [10] revealed that it belongs to the β-coronavirus genus, with 79.0 % nucleotide identity to SARS-CoV and 51.8 % identity to MERS-CoV. Inoculation with SARS-CoV-2 of human airway epithelial cells *in vitro* causes cytopathic effects [10] and cessation of the cilium beating of epithelial cells, similar to the cytopathic effect observed for SARS-CoV infection [13]. The initial step in viral infection was revealed by the crystal structure of SARS-CoV-2 spike receptor binding domain [14], which, just as SARS-CoV [15], binds to the host cell receptor angiotensin-converting enzyme 2 (ACE2). The presence of ACE2 on the cell membrane is crucial for virus virulence, as HeLa cells, lacking ACE2, are resistant to SARS-CoV-2 infection [16,17]. Structural analysis identified residues in the SARS-CoV-2 spike receptor binding domain that are critical for ACE2 binding, the majority of which either are

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highly conserved or share similar side chain properties with those of SARS-CoV. These similarities in virus entry between SARS-CoV-2 and SARS-CoV correlate with detectable cross-neutralizing activity of serum from SARS-CoV-recovered patients [18]. However, no available monoclonal antibodies targeting SARS-CoV receptor binding domain were able to prevent SARS-CoV-2 infecting the cells, highlighting unique intrinsic structure features of SARS-CoV-2 S-protein binding domain, including a much higher binding affinity than that of SARS-CoV S-protein [19]. In line with this, more recent study reports that human recombinant soluble ACE2 effectively, but not completely prevents SARS-CoV-2 infection, suggesting alternative mechanisms for viral entry [20].

Surface molecule CD147 (EMMPRIN or Basigin) is being considered as one alternative pathway for the virus to enter the host cells, since SARS-CoV-2 S-protein can bind CD147 as suggested by preliminary data [21]. CD147 is expressed on hematopoietic cells, including red blood cells, epithelial and neuronal cells [22]. Basigin is viewed as the molecular gate for plasmodium *P.malariae* [23]. Not surprisingly, CD147 is also associated with the HIV1 [24] and SARS-CoV [25] infections. In both cases, viral protein binds to the CD147 in complex with cyclophilin A (CyPA). SARS-CoV N-protein conjugates with CyPA inside ACE2-expressing infected host cells [25]. With this modification, newly assembled viral particles can infect CD147-positive cells. However, further studies are needed to evaluate possible impact of SARS-CoV-2 interaction with Basigin in the context of COVID-19.

ACE2, crucial for SARS-CoV-2 virulence, is expressed in the upper and the lower respiratory tract, most remarkably on lung alveolar epithelial cells, arterial and venous endothelial cells, as well as enterocytes of the small intestine, epithelial cells in the kidney. ACE2 expression is also detected in heart, pancreas, testis and brain [26]. Interestingly, ACE2 expression is not the highest in the upper respiratory tract [27,26], once again, supporting the hypothesis that increased transmissibility of SARS-CoV-2 as compared to SARS-CoV may be attributed to yet to be identified co-receptors or auxiliary factors adopted by SARS-CoV-2 [28]. Also, the fact that ACE2 is widely expressed in other tissues and organs explains a broad spectrum of adverse effects not limited just to the lungs. In addition, it was shown that SARS-CoV-2 directly infects ACE2-expressing tissue-resident $CD169^+$ macrophages in the spleens and LNs, causing lymph follicle depletion, splenic nodule atrophy, histiocyte hyperplasia and lymphocyte reduction [29]. Thus, virus infection of macrophages, firstly, enhances viral spread and, secondly, triggers destructive events in the immune organs such as spleen and LNs. Recent data from the experiments using SARS-CoV-2 capsid or live virus infection of cultured T cell lines (MT-2 and A3.01) provides first evidence that SARS-CoV-2 could also infects T cells. However, expression level of ACE2 on T cells is low and, thus, CD147 is considered to mediate SARS-CoV-2 entry into T cells [17].

After virus binds to ACE2 (Fig. 1), serine protease, TMPRSS2, cleaves the viral spike protein. Then another protease, Furin, subsequently releases spike fusion peptide, and the virus enters the host cell through an endosomal pathway [18,30,31]. Following viral replication, assembly and release, the infected cells may undergo apoptosis or necrosis, triggering the inflammatory response with production of pro-inflammatory cytokines and activation of macrophages and Th1 cells, as well as production of IFNγ, IL-17A, IL-21, and IL-22 by neutrophils, Th17 and $CD8^+$ cells. In turn, SARS-CoV-2 infection of recruited immune cells may increase their apoptosis and exacerbate lymphocytosis [32,33], and, finally, may lead in some patients to life-threatening conditions, such as respiratory distress syndrome, cytokine storm, and secondary hemophagocytic lymphohistiocytosis.

COVID-19 mortality is strongly associated with the development of severe respiratory distress syndrome, which requires invasive ventilation. It is important to identify those patients who are most likely to develop a severe form of the disease as early as possible. Based on the existing statistics, a number of clinical predictors of the disease deterioration and mortality, including the presence of secondary infections, lymphopenia [34], comorbidities such as cardiovascular and chronic respiratory diseases, diabetes, hypertension, obesity and cancer [35], increased cytokine production and serum ferritin [36] have been reported. The other study showed that the elevated serum creatinine, D-dimers, lactate dehydrogenase, C-reactive protein, procalcitonin, as well as increased white blood cell counts may indicate impending respiratory failure and the need for invasive oxygen supply [37]. Interestingly, in recently published reports elevated interleukin-6 (IL-6) level was proposed as a relevant parameter predicting the unwanted course of the disease and the need for mechanical ventilation [38–40]. These assumptions are consistent with data from a clinical trial in China that demonstrated on a small number of patients the efficacy of IL-6 neutralization during exacerbation of COVID-19 associated pneumonia [41] (Supplementary Table 1).

IL-6 is a cytokine with pleotropic functions ranging from hematopoiesis and metabolic regulation to inflammation, autoimmunity and acute phase response. IL-6 modulates host defense through a number of immune stimulating mechanisms: control of monocytes and their differentiation into macrophages [42], modulation of antigen-dependent B cell differentiation [43], increased IgG production by B cells [44], and promotion of Th2 response by inhibiting Th1 polarization [45]. Several studies revealed strong correlation between IL-6 levels in the serum and the upcoming respiratory failure [46–48]. It was shown, that even moderately elevated IL-6 levels above 80 pg/mL were sufficient to identify COVID-19 infected patients with a high risk of respiratory failure [37]. Moreover, serum SARS-CoV-2 nucleic acid (RNAaemia), which is strongly associated with cytokine storm, is closely correlated with extremely high IL-6 serum levels [47]. It was also suggested that

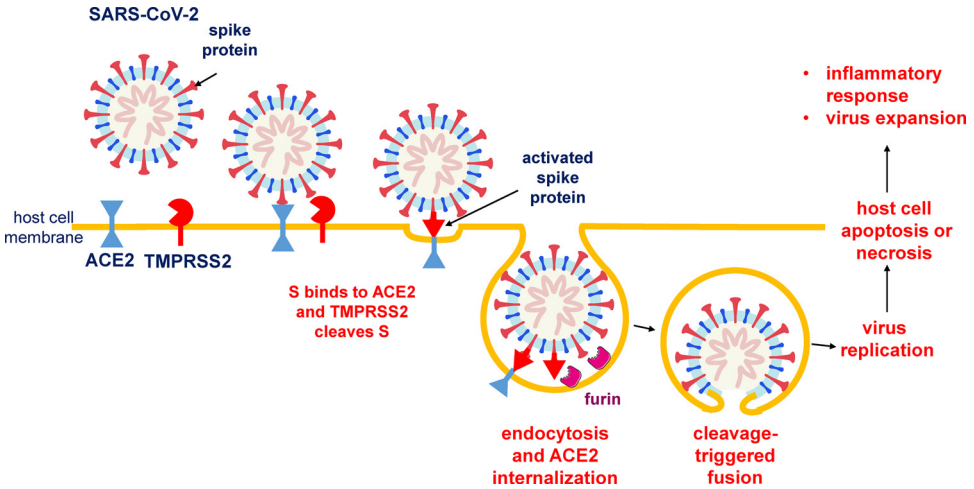

Fig. 1. Schematic representation of SARS-CoV-2 interaction with a target cell.
Binding of virion to ACE2 is followed by serine protease, TMPRSS2, cleavage of the viral spike protein and induction of internalization of the complex with subsequent reduction of ACE2 surface availability. Then another protease, Furin, releases spike fusion peptide, and the virus enters the host cell through an endosomal pathway.

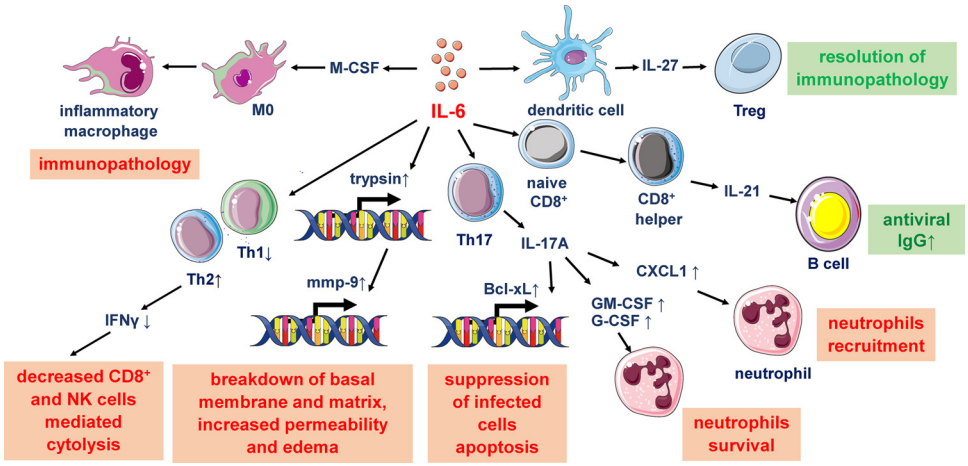

Fig. 2. Role of IL-6 in respiratory viral infections.
IL-6 demonstrates opposing effects during the immune response to viral infections in the lungs. IL-6 promotes highly specific reaction of adaptive immunity by stimulating of $CD8^+$ T cells and B cells, which is balanced by T regulatory cells. Also, IL-6 facilitates survival of phagocytic neutrophils. On the other hand, IL-6 can provide unfavorable Th2 and Th17 over Th1 helper differentiation and facilitate tissue injury by dysregulation of extracellular matrix and attraction of neutrophils and pro-inflammatory macrophages.

serial measurement of circulating IL-6 might be important in identifying disease progression or, when evaluated immediately after COVID-19 diagnosis confirmation, may predict the upcoming respiratory failure or, alternatively, asymptomatic disease among SARS-CoV-2 infected patients [49].

Therefore, it would be valuable to explore the potential contribution of IL-6 in the events occurring during SARS-CoV-2 infection. The next section will discuss the mechanisms by which IL-6 may possibly affect the disease exacerbation and the potential of therapeutic approaches based on anti-IL-6 biologics.

3. Controversy concerning IL-6 functions during viral lung infections

IL-6 is one of the key proinflammatory cytokines during infection onset, especially, at the mucosal sites [50]. However, the impact of IL-6 on the disease outcome may vary significantly (Fig. 2). On one hand, IL-6-dependent Th17 activation and differentiation are important for effective neutrophil migration, IL-6 together with IL-15 modulate cytolytic capacity of $CD8^+$ T cells [51,52], and, finally, IL-6, as a pyrogenic cytokine, contributes to thermostatic regulation which is important for effective anti-viral response [53,54]. Studies, using IL-6-deficient mice, showed that IL-6 ameliorates acute lung injury in influenza A virus (IAV) infection [55]. IL-6-deficient mice infected with influenza virus exhibited higher lethality, as well as increased weight loss and fibroblast accumulation in the lungs associated with virus-induced apoptosis of lung epithelial cells and neutrophils [56] indicating that IL-6 may promote repair following virus-induced lung injury [57]. Finally, early IL-6 signaling promotes IL-27-dependent maturation of Treg cells in the lungs and resolution of viral immunopathology in mouse model of respiratory syncytial and influenza virus infection [58].

On the other hand, IL-6 has been implicated in the progression of viral infections. In this regard, IL-6 synergizes with IL-1b and TNF to upregulate trypsin expression, which activates matrix metalloproteinases and causes the breakdown of basal membrane and extracellular matrix, which, in turn, results in increased tissue permeability and edema [59]. Th1 cell-derived IFNγ is essential for effective antiviral immune response. However, IL-6 may inhibit Th1 polarization by stimulating $CD4^+$ cells to differentiate into Th2 cells or by suppressing IFNγ expression [60,61]. Moreover, IL-6 promotes Th17 cell differentiation and IL-17A secretion, which, in turn, activates the expression of anti-apoptotic molecules, such as Bcl-X_L, favoring survival of virus-infected cells in the model of persistent viral infection [62]. At the same time, IL-17 promotes the migration [63], and survival [64] of neutrophils which, in turn, contribute to the pathogenesis of COVID-19-driven ARDS [65]. Finally, in contrast to influenza virus infection, IL-6-deficient mice infected with murine pneumonia virus are characterized by better survival than WT mice with decreased lung edema and diminished neutrophil recruitment [66].

Taking into account that in several experimental models of viral lung infections IL-6 demonstrates either pathogenic [66] or protective [55] effects in vivo, the role of this cytokine in SARS-CoV-2 infection should be carefully evaluated. Moreover, the consequences of IL-6 induction in COVID-19 may vary depending on the infection stage and on the host immune status.

4. SARS-CoV-2-associated cytokine release syndrome

Patients with the most severe outcome of SARS-CoV-2 displayed high serum levels of proinflammatory cytokines responsible for cytokine storm induction [36,67]. Interestingly, the majority of severe COVID-19 cases with respiratory distress syndrome were associated with high systemic IL-1b, TNF and IL-6 levels, suggesting a direct connection between proinflammatory cytokine induction and adverse effects of COVID-19 [34]. As SARS-CoV-2 shows 79 % nucleotide identity to SARS-CoV, major pathogenic mechanisms, including cytokine storm and extensive lung damage during SARS and COVID-19 infection may be similar. Cytokine storm is a condition caused by extensive activation of the immune system, and, as a result, extremely high production of cytokines and chemokines. Since cytokine storm can lead to multiple organ failure, it is important to understand the mechanisms driving this condition.

In lower respiratory tract SARS-CoV-2 infects predominantly type 2 alveolar epitheliocytes, the cell type which does not participate in active gas exchange. Following replication and disengagement of the lung epithelial layer, virus enters the underlying tissues and infects or is being captured by macrophages, dendritic cells and neutrophils, resulting in further viral spread [29] (Fig. 3). At the same time, damaged epitheliocytes release danger molecules which drive the activation of lung epithelium and resident immune cells. Thus, even at the early onset of viral infection, its penetration of the mucosa to the epithelial layer activates the innate immune response. Adaptive immunity is also activated during COVID-19, mainly by antigen presenting dendritic cells, which produce large amounts of cytokines, including IL-6, IL-1b and TNF and migrate to the regional lymph nodes to present viral antigen to naïve T cells, pushing their differentiation and migration into the affected tissue [68]. Specific humoral response represented by viral-specific antibody-producing B cells is also in place [69]. Replication of the virus results in further damage of affected organs together with self-boosting immune response manifesting to uncontrolled overexpression of inflammatory mediators in severe cases. Another mechanism driving cytokine storm during viral infections is increased blood vessel permeability which enables infiltration of effector cells, producing additional amounts of inflammatory molecules and exacerbating hyper

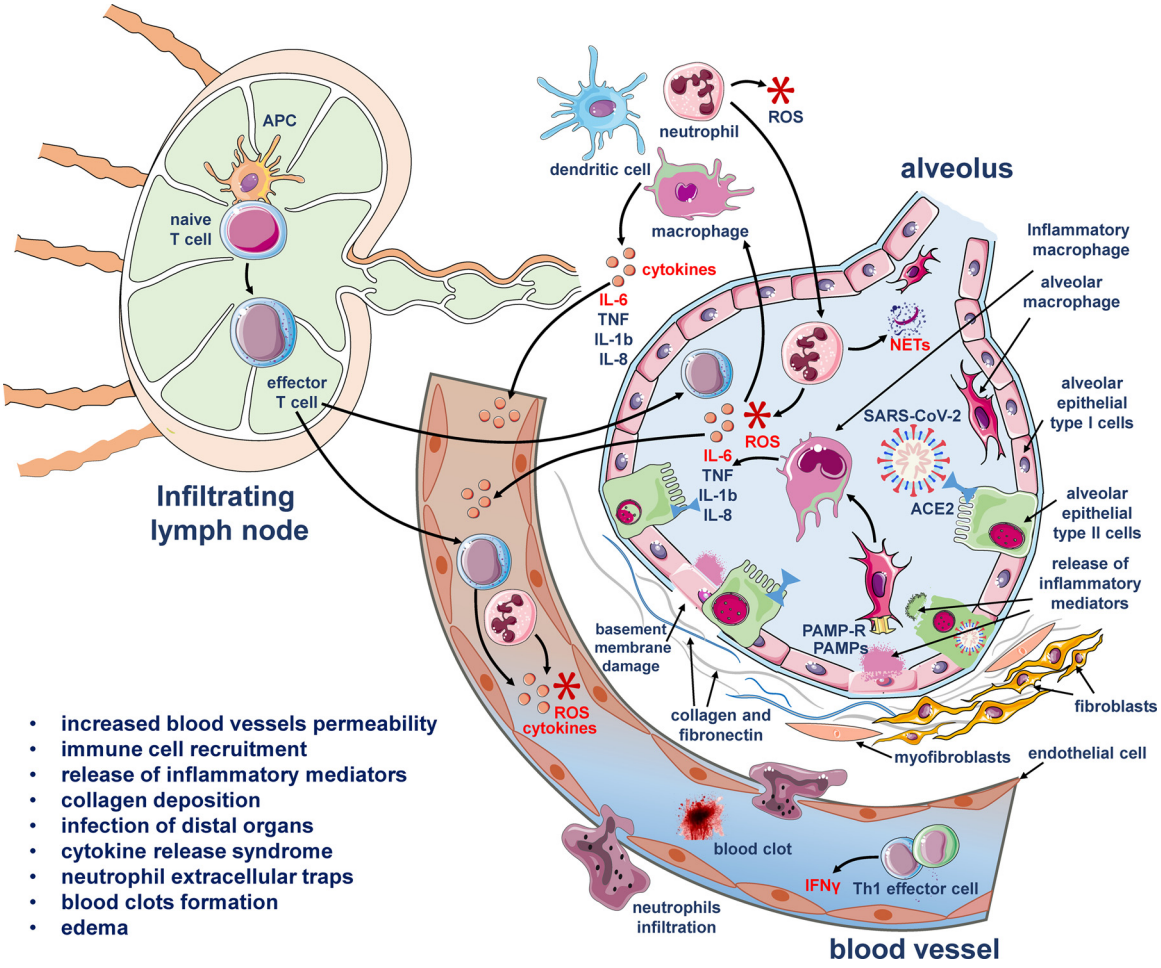

Fig. 3. Cytokine release syndrome in COVID-19.
SARS-CoV-2 replicates in alveolar epithelial cells. After the virions are released, they can infect or are being captured by macrophages, dendritic cells and neutrophils. At the same time, damaged epithelial cells produce alarmins, which are sensed by the neighboring epithelial and myeloid cells. All these events lead to release of proinflammatory cytokines, increase of alveolar vessel permeability and cell recruitment to the site of infection, forming positive loop for pathological activation of IL-6, IL-1, TNF and other proinflammatory cytokines. Due to high permeability of pulmonary vessels under inflammatory conditions, SARS-CoV-2 can inseminate distant ACE2-expressing tissues (intestine, kidney, pancreas), and trigger burst of inflammation at distant sites.

cytokine production [70]. In addition, leakiness of blood vessels allows virus to spread to other tissues and organs, compromising their functions. Finally, under persistence of inflammatory factors, an increased number of inflammatory exudates and erythrocytes enter the alveoli, resulting in lung damage and respiratory failure syndrome.

As mentioned above, severe COVID-19 induced pneumonia is marked by hyperactivation of the immune system and excessive production of IL-6 [36,67]. The main source of pathogenic IL-6 appears to be myeloid cells as their number is significantly increased among PBMC [69] and in BALF of severe COVID-19 patients [71]. Myeloid cell recruitment and activation in the lungs is associated with increased mortality and morbidity in SARS-CoV mouse model [72]. Human primary macrophages and dendritic cells can be infected, but they fail to support productive replication of SARS-CoV [73,74], unlike alveocytes, in which virus can replicate very quickly. At the same time, SARS-CoV and, apparently, SARS-CoV-2-infected macrophages demonstrate up-regulation of IL-6 production and low expression of interferons [29,73]. Interestingly, patients requiring intensive care and invasive lung ventilation display negative correlation between IL-6, TNF and IL-1b concentrations and $CD4^+$ and $CD8^+$ T cell counts [75], confirming previous studies in animal models, which suggested that cytokine storm actually dampens adaptive immunity against SARS-CoV infection [76]. Moreover, production of IFNγ by $CD4^+$ T cells tended to be lower in severe as compared to moderate cases, suggesting that SARS-CoV-2 infection induces lymphopenia with the suppression of antiviral IFNγ production [36]. Furthermore, it has been suggested that this pathogenic IL-6 is likely to be produced by highly inflammatory macrophages [71], but not by alveolar macrophages, which are almost absent in the lung aspirates of severely affected patients [77]. At the same time, it should be noted that complete ablation of IL-6 at the very early stages of viral infection may result in depressed Tfh cell maturation and delayed antiviral antibody response [78].

It is known that acute inflammation and cytokine storm, as its extreme manifestation, can have a significant effect on hemodynamics and also on platelets and erythrocytes. The dysregulated coagulation cascade and the subsequent formation of intra-alveolar or systemic fibrin clots are prominent findings in previous zoonotic coronavirus infections (SARS and MERS) orchestrated by CRS [79–81]. COVID-19 patients also show significant changes in coagulative status (i.e. low platelet count, increased D-dimer, fibrinogen levels) and dysfunction of micro-vessels in pulmonary circulation [82,83], thus, thrombosis of the pulmonary capillaries is believed to contribute to rapidly developing hypoxia. The role of IL-6 in inflammatory hypercoagulation is controversial: IL-6 can increase the rate of fibrotic clot formation in whole blood, but the effect is less pronounced than it is shown for IL-1 or IL-8 [84]. On the other hand, IL-6 is important for thrombus formation being a regulator of MMPs and other thrombolysis-associated genes in macrophages [85].

Other characteristic feature of cytokine release syndrome is change in iron homeostasis and hyperferritinemia as indicated by high levels of serum ferritin [86]. In COVID-19 patients ferritin elevation correlated with poor prognosis [36], as it was an indication of hemolytic events caused by hypercoagulation and hemophagocytosis. In general, inadequate macrophage activation leads to pathologic phagocytosis of erythrocytes and reutilization of heme iron using ferritin [87]. In line with this, high systemic ferritin may serve as an indicator of developing macrophage activation syndrome, rather than a factor driving COVID-19 pathogenesis.

Another key proinflammatory cytokine, TNF, is also released abundantly during cytokine storm, caused by SARS-CoV-2 infection. Serum TNF levels were found to be elevated in severely affected COVID-19 patients [34]. Previously, it was shown for SARS-CoV that its spike protein is able to modulate TNF converting enzyme (TACE)-dependent shedding of the ACE2 ectodomain [88]. TACE expression is coupled to TNF production. Therefore, it is hypothesized that the use of TNF inhibitors may also show some efficacy in preventing viral entry [89], as well as in decreasing immunopathology associated mortality, as it was shown in preclinical studies in mice infected with severe respiratory syncytial virus [90]. Moreover, anti-TNF therapy was effective in decreasing the IL-6 and IL-1b serum levels in lethal bacteremia, suggesting that such treatment may provide complex anti-inflammatory effect [91]. Data obtained from COVID-19 infected patients with inflammatory bowel diseases undergoing anti-TNF therapy support safety of such intervention in the context of SARS-CoV-2 treatment [92,93]. These findings argue for a potentially protective effect of TNF inhibition in COVID-19 and further studies are needed to address this possibility.

5. ACE2 downregulation may induce IL-6 production in Angiotensin II-dependent manner

Hypertension has been suggested as a risk factor for severe COVID-19 outcomes [94]. Early data from the literature already assumed an association between blood pressure and circulating IL-6 levels in otherwise healthy individuals [95]. Moreover, several studies reported an increased IL-6 expression in patients with hypertension [96,97]. IL-6-transgenic mice, characterized by elevated plasma IL-6 levels, displayed pulmonary hypertension [98,99]. Taken together, this data suggest that IL-6 might be connected with increased risk of respiratory failure in hypertensive patients with COVID-19.

One of the mechanisms regulating blood pressure and electrolyte balance is angiotensin-renin system. It is comprised of two pathways, which are normally functioning in the state of dynamic equilibrium: ACE2-Angiotensin II–Angiotensin 1 Receptor axis, activating vasoconstriction and inflammatory response, and ACE2-Angiotensin 1–7-Mas receptor axis, supporting vasodilation and suppression of inflammation (Fig. 4, A) [100]. Changes in renin-angiotensin system activity are related to the pathogenesis of hypertension and of inflammatory lung diseases, in particular, acute lung injury caused by viral infections [15,101].

SARS-CoV2 uses ACE2 as an entry site, thus, reducing ACE2 availability, promoting an imbalance between the ACE2-Angiotensin II–Angiotensin 1 receptor axis and the ACE2- Angiotensin 1–7-Mas receptor axis [15,102]. In line with this, recent studies have reported that COVID-19 patients have increased Angiotensin II compared to healthy individuals [103]. Altogether, the abovementioned data suggests that COVID-19 infection leads to imbalanced angiotensin conversion and a shift towards pro-inflammatory signaling mediated by Angiotensin 1 receptor axis [104] (Fig. 4, B).

Angiotensin II is known to significantly increase the expression of IL-6 in a dose-dependent manner [105] through pleiotropic activation of NF-kB transcription factors [106,107]. Angiotensin 1 receptor downstream activation of NADPH oxidase results in elevated oxidative stress, in particularly, superoxide that activates transcriptional mechanisms that directly promotes IL-6 gene expression. In turn, plasma IL-6 concentrations correlate with blood pressure, plasma Angiotensin II levels and vascular hypertrophy, suggesting an important role of IL-6 in the development and maintenance of hypertension, specifically, that mediated by Angiotensin II [108,109]. IL-6 promotes Angiotensin 1 receptor expression sensitizing the vascular wall to angiotensin II-dependent signaling mechanisms. Activated cells can release cytokines, including IL-6, which promote expression of adhesion molecules and induce endothelial activation, inflammatory cell infiltration and vascular inflammation [110]. This further drives oxidative stress and IL-6 expression. Therefore, it is plausible that IL-6 and Angiotensin II activate each other through a positive feedback mechanism. In support of this hypothesis, ACE2 protects against lethal avian influenza A H5N1 infection [111] through prevention of oxidative stress and acute respiratory distress syndrome. Moreover, it was recently reported that in COVID-19 patients with hypertension Angiotensin receptor blockade attenuated the inflammatory response, possibly through IL-6 inhibition [102,112]. Taking together, Angiotensin II accumulation due to SARS-CoV-2-mediated ACE2 downregulation may cause Angiotensin 1 receptor downstream activation of NADPH oxidase, which, in turn, leads to elevated ROS production and to induction of transcriptional mechanisms that directly promote IL-6 expression, implicated in inflammation-induced injury and immunopathology.

6. Risk factors associated with COVID-19

Chronic inflammation is the one common feature of hypertension, diabetes, obesity and age – the risk factors associated with COVID-19 severe outcomes. Elderly, obese and diabetic persons are affected by a low-grade chronic inflammation and are characterized by systemically increased levels of proinflammatory cytokines, which may contribute to and facilitate the cytokine storm, the main cause of COVID-19 mortality.

Among conditions, predisposing patients infected with SARS-CoV-2 to severe outcomes, diabetes is the most prominent. It is estimated that mortality rate of those with COVID-19 and diabetes is about 16 % [8] to 35 % [113]. IL-6 is known for its dual role in autoimmune diabetes, as it is involved in the development of insulin resistance and β-cell dysfunction and, at the same time, has anti-inflammatory effects and improves glucose metabolism [114]. Recent clinical data demonstrates significantly elevated systemic IL-6 in COVID-19 patients with diabetes as compared to those without diabetes [115]. COVID-19 may exacerbate the pre-existing diabetes, since its entry site, ACE2, is expressed in the pancreas, with a potential role in the development of insulin resistance and impaired insulin secretion [116]. IL-6 may be the link between diabetes and severe COVID-19 outcomes through its ability to modulate T cell response. Some indirect evidence to support this comes from mouse studies of closely related MERS-CoV infection demonstrating that abnormal elevation of IL-17A produced by IL-6-dependent Th17 cells exacerbates disease severity in diabetic mice [117]. Consistent with that finding, patients with COVID-19 have a higher proportion of Th17 cells in the blood [118], suggesting that diabetics due to improper activation of Th1 and Th17 cells may have a compromised anti-viral immune response [31].

Obese patients with COVID-19 are more likely to develop severe respiratory distress syndrome [119,120]. Just as diabetics, obese patients have higher concentration of proinflammatory cytokines both in steady state [121] and, apparently, during COVID-19 infection [8]. In addition to decreased anti-viral T cell response, enhanced IL-6 production by adipose tissue in obese patients [122] may alter innate antiviral immune response by neutrophils [121] and cause uncontrolled replication of the virus at the early stages of infection.

From the very beginning of COVID-19 pandemic, age was identified as a risk factor [38], supporting the idea that ACE2 may be a marker of cell senescence [123]. Myofibroblasts, which increase in number with age, express high levels of ACE2 [124], thus, myofibroblasts are more susceptible to SARS-CoV-2, and elderly people, bearing higher

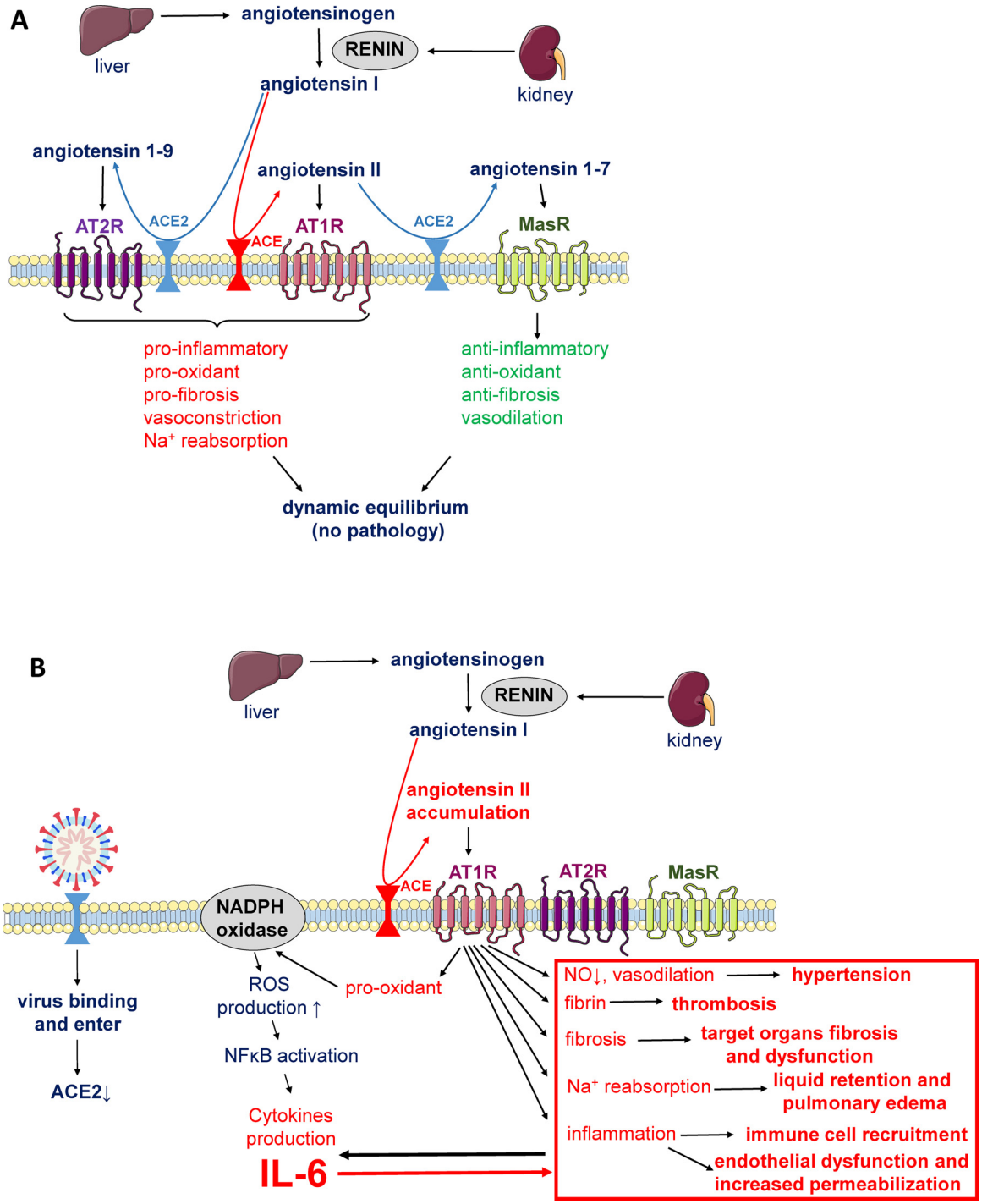

Fig. 4. ACE2 downregulation may drive IL-6 production in Angiotensin II-dependent manner.
A – in healthy state pro-inflammatory signaling of Angiotensin II via Angiotensin 1 receptor (AT1R) is stabilized by Angiotensin 1–7 (ACE2-Angiotensin I proteolysis product) signaling via Mas receptor (MasR) that has anti-inflammatory effect.
B – virus-mediated down-regulation of ACE2 leads to Angiotensin II accumulation in the absence of Angiotensin 1–7 and acceleration of its proinflammatory effect. AT1R downstream activation of NADPH oxidase results in elevated ROS directly promoting IL-6 expression. In its turn, IL-6 can positively regulate AT1R levels. Thus, by acting together these processes exacerbate hypertension, edema, infiltration of immune cells and inflammation in COVID-19 affected lungs.

proportion of myofibroblasts, might be more susceptible to COVID-19 infection (reviewed in [125]). IL-6 is a critical inflammatory regulator of senescence-associated secretory phenotype (SASP) [126]. Therefore, IL-6 overexpression may correlate both with senescent status of cells and tissues, as well as with increased expression of ACE2. In line with this idea, hydroxychloroquine, an anti-malaria drug, which is now approved in some countries for COVID-19 treatment, effectively reduced the salivary and serum levels of IL-6 in patients with Sjorgen's syndrome [127]. Moreover, azithromycin, prescribed together with hydroxychloroquine, can target and selectively remove senescent cells [128] and, thus, provide anti-fibrotic activity by protecting the lungs from inflammation-induced injury [129,130].

Another issue facing elderly patients with COVID-19 is a compromised activation status of their effector T cells. These cells may display limited function during prolonged infection as a result of their exhaustion, associated with the surface expression of such immune-

inhibitory factors as PD-1 [75]. Since aging itself is a process known to promote reorganization of the T cell landscape [131] and IL-6 is a SASP predictor and regulator, T cell exhaustion in the elderly patients with COVID-19 is much more evident due to higher basal concentration of IL-6, which can enhance the exhaustion process [132,133].

Smoking is another potential risk factor for SARS-CoV-2 infection. Smokers are more vulnerable to influenza virus infections [134,135] and are more likely to develop chronic obstructive pulmonary disease (COPD) [136]. Enhanced ACE2 expression had been reported in the lungs of healthy smokers [137,138]. In line with that, studies in mice have established that cigarette smoke can trigger the expansion of a subpopulation of respiratory epithelial cells that express ACE2 in a dose-dependent manner [139]. Patients with COPD, as well as active smokers, have increased ACE2 expression in the lungs [140], which may potentially explain a fourfold increased risk of adverse development and severe outcome of COVID-19 [141,142]. Taken together, these recent reports suggest that smokers may be at higher risk of infection. Examination of factors, predisposing to severe COVID-19 in Wuhan, China, revealed, that 19.2 % of patients with severe disease were smokers [143]. On the other hand, preliminary meta-analysis based on Chinese patients suggest that active smoking was not associated with the severity of COVID-19 [144], indicating that impact of smoking on COVID-19 progression is controversial and requires further assessment.

Intuitively, patients with pre-existing asthma should display higher proportion of COVID-19 severe cases. However, the prevalence of asthma in COVID-19 patients in Wuhan study was markedly lower (0,9%) than that reported in the adult population of Wuhan (6,4%) [143]. One possible explanation is a shift toward Th2-type immune response in asthmatics as opposed to Th1-associated inflammatory response induced by SARS-CoV-2 infection [118]. Recent study reveals that TMRSS2 expression in upper respiratory tract correlates positively with type 2 response genes, especially with IL-13, whereas ACE2 expression is suppressed by IL-13. Considering low numbers of cells co-expressing these proteases in the upper respiratory tract, it has been proposed that in the context of IL-13-dependent reduction in ACE2 expression allergy should promote resistance to infection [145]. In line with this, it was shown that ACE2 expression is decreased in nasal and bronchial epithelium of allergic individuals following allergen challenge, suggesting, that asthma-associated immune response actually protects from COVID-19-induced pathology [146]. Nevertheless, further studies are required to reveal the impact of COVID-19 severity in patients with preexisting asthma.

Meta-analysis studies of COVID-19 cases in China from December 2019 to February 2020 report lower incidence of the disease [147] and risk of death [35] in women than in men. Similar data on association of gender with poorer prognosis for males were obtained earlier for SARS-CoV [148,149], and MERS-CoV [150,151]. In connection to SARS-CoV-2, the X-linked *ACE2* gene is of a particular interest. Significant fraction of genes encoded on the X chromosome undergo dosage compensation, however, *ACE2* is located at Xp22, i.e. the area in which genes may escape from X chromosome inactivation [152], possibly contributing to gender disparity in disease susceptibility. Gender differences in immune responses are known to depend not only on genetic, but also on endocrine factors [153,154]. High doses of estradiol acting through estrogen receptors decrease production of proinflammatory cytokines via suppressing NF-kB signaling pathway [155]. In relation to COVID-19 the effects of estrogens on IL-6 and on disease progression is of particular interest. Estrogen may suppress LPS-mediated IL-6 expression in mouse macrophages by both blocking of NF-kB activation [155,156] and inhibiting p38 MAPK phosphorylation [156]. Furthermore, down-regulation of IL-6 expression in Kupffer cells appears to be ERα-dependent [157]. Overall, immunomodulatory effects of estrogens may contribute to decreased susceptibility to SARS-CoV-2 infection in women and this question requires further study.

7. The aftermath of COVID-19 infection

One of the common complications from the respiratory viral infections, including SARS [158] and COVID-19 [159], is lung fibrosis. This is characterized by alveolar epithelial cell injury, recruitment and activation of fibroblasts and subsequent production of extracellular matrix (ECM) in the presence of specifically activated immune cells. Fibrosis develops as an exaggerated repair process following injury associated with abnormal immune response leading to chronic progressive disease [160]. Histological examination of lung biopsies from COVID-19 patients show massive apoptosis of pneumocytes, hyaline membrane formation, fibromyxoid exudates [161] which are manifestations that are characteristic for ARDS and represent key events preceding development of fibrosis (reviewed in [162]). Significant pro-fibrotic M2-like SPP1^{+}macrophage infiltration was also described for COVID-19 correlating with the disease severity [71]. Damage to the epithelial layer caused by the virus further attracts various immune cells participating in inflammation-repair balance (monocytes, macrophages, granulocytes and T cells). In addition, some viral components, such as N-protein and papain-like protease, can directly stimulate production of TGF-β, one of the pro-fibrotic hallmarks in respiratory epithelium, similar to what has previously been reported for SARS-CoV [163,164].

The role of IL-6 had been extensively studied in bleomycin model of lung fibrosis in mice. Bleomycin is a chemotherapeutic antibiotic which causes damage of tissues lacking bleomycin hydrolase, predominantly, in the lungs [165]. Mice with genetic ablation of IL-6 were characterized by impaired fibrosis [166]. However, in the same model mice with pharmacological rather than genetic inhibition of IL-6 demonstrated opposing phenotypes depending on the phase of inflammation-repair cycle. Specifically, IL-6 neutralization at the early inflammatory phase (day 2 following bleomycin-induced lung injury) resulted in apoptosis of pneumocytes, which further contributed to pulmonary fibrosis, whereas IL-6 blockade at the early fibrotic stage (day 8 following bleomycin-induced lung injury) significantly ameliorated lung fibrosis [167]. Interestingly, treatment of mice with recombinant soluble gp130Fc at the late stage of chronic bleomycin model attenuated lung fibrosis, emphasizing the importance of sIL-6Ra and IL-6 trans-signaling in mediating this condition [168]. It was further suggested that M2-like infiltrating macrophages are the major source of soluble IL-6Ra in fibrotic foci, whereas pulmonary fibroblasts are the recipient cells, which proliferate and produce extracellular matrix under trans-IL-6 activation. Finally, overexpression of IL-6 in respiratory tract mediated by adenoviral vectors also resulted in the exacerbation of fibrosis and was associated with increased levels of M2-macrophages with pro-fibrotic features [169]. These pro-fibrotic macrophages are also characterized by increased IL-6Ra expression [168]. ACE2 expression is reported for lung, heart, kidney, intestine, liver and brain. Thus, similar fibrosis-associated complications should be expected, not just for respiratory tract, but also for other tissues and organs in correlation with viral load and severity of cytokine release syndrome. Summarizing the data available at the moment from infection-free experimental models of fibrosis, one can conclude that IL-6 may affect fibroblast proliferation and functions directly or through potentiation of a distinct macrophage phenotype. Taking into account the importance of this cytokine at the repair stage, anti-IL-6 therapy may prove beneficial not only in acute phase, but also in subacute proliferative phase of COVID-19-related ARDS.

SARS-CoV-2 tropism to neural system is of particular interest while neurological symptoms, such as dizziness, headache, ataxia and anosmia, are often found in mild COVID-19 patients and develop early in the infection [170]. ACE2 expression in CNS is attributed to the nuclei in brain stem and is associated with cardio-respiratory control [171,172]. Recent study based on scRNA sequencing suggests co-expression of ACE2 and TMPRSS2 in olfactory epithelial cells, but not in mature olfactory sensory neurons, which were initially considered as

the most obvious target population for the virus in CNS [173]. Even without the understanding of the exact mechanisms of SARS-CoV-2 penetration and distribution in CNS, it should be noted that as a result of the disseminated intravascular coagulopathy and cytokine storm caused by infection, blood-brain-barrier permeability is significantly increased, which can lead to negative consequences for CNS functioning [174,175].

8. Therapeutic potential of IL-6 inhibitors

An effective therapeutic approach should include a combination of specific antiviral drugs, which inhibit viral dissemination and limit direct virus-induced cytopathic effects coupled with anti-inflammatory therapeutics, directed against immunopathology induced by a viral infection [176]. SARS-CoV-2-induced immunopathology exhibits features of systemic hyper-inflammation reminiscent both of cytokine storm or macrophage activation syndrome and secondary haemophagocytic lymphohistocytosis [177]. Since overexpression of IL-6 appears to be associated with severe COVID-19 outcomes, neutralizing antibodies used to treat a number of autoimmune diseases by targeting exacerbated inflammatory immune response of the host may provide a life-saving approach by preventing the cytokine release syndrome. In line with that, patients responding to CD19 CAR T cell therapy experience cytokine release syndrome [178], which is well managed by IL-6 neutralizing antibodies [179]. In a non-randomized, open-label clinical trial, 21 patients with severe or critical COVID-19 were treated with a single dose of Tocilizumab, in addition to routine therapy [180]. 90 % of patients recovered, suggesting that anti-IL-6 might be a powerful potential rescue therapy in managing acute respiratory distress syndrome of COVID-19 and inhibiting the most adverse outcome. Peripheral mononuclear cell scRNA-seq profiling data obtained from these patients indicate that treatment with Tocilizumab does not reduce the number of cytotoxic $CD8^+$ and plasma B cells, thus, does not interfere with robust adaptive immune response [69]. Preliminary data from 21 patients with COVID-19 who developed acute respiratory distress syndrome and participated in a compassionate-use program at Papa Giovanni XXIII hospital in Bergamo, Italy, indicate that intravenous introduction of Siltuximab reduced C-reactive protein level in all patients and significantly improved clinical conditions with a reduced need for ventilation in 33 % of patients. 43 % of patients showed stabilization of their conditions, and 24 % of patients experienced a worsening of the disease and required intubation [181].

Sarilumab is a monoclonal antibody that works by inhibiting the IL-6 pathway through binding and blocking the IL-6 receptor. Recently, another clinical trial was initiated, which will evaluate the effects of Sarilumab in patients with severe COVID-19. This U.S.-based multicenter, double-blind, phase 2/3 trial will begin at medical centers in New York and is anticipated to enroll up to 400 patients [182].

The overview of initiated clinical trials of anti-IL-6 therapeutics in COVID-19 patients is presented in Supplementary Table 1. In summary, strong scientific evidence of the beneficial impact of IL-6 inhibitors in the modulation of the COVID-19 infection requires further clinical data.

9. Conclusion

In the face of a pandemic, affecting millions of people worldwide, the need to develop new approaches or reassess the existing ones in the treatment of severe viral infections is more pressing than ever. Despite the fact that humanity experienced viral infections causing deadly pneumonia twice in the past 20 years, there are still no drugs specific for coronaviruses. The evidence discussed in this review suggests that for patients with risk factors, especially those with high systemic levels of IL-6, clinically approved neutralizing antibodies against IL-6 or its receptor, IL-6R, in combination with standard treatment protocols may provide benefit. Gaining a deeper understanding of the factors that influence the immune response and providing a mechanistic link of these factors to disease severity is crucial for the successful clinical management of COVID-19 in severely affected patients.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cytogfr.2020.05.009.

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