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## Review article

# Protective role of ACE2 and its downregulation in SARS-CoV-2 infection leading to Macrophage Activation Syndrome: Therapeutic implications

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## ABSTRACT

In light of the outbreak of the 2019 novel coronavirus disease (COVID-19), the international scientific community has joined forces to develop effective treatment strategies. The Angiotensin-Converting Enzyme (ACE) 2, is an essential receptor for cell fusion and engulfs the SARS coronavirus infections. ACE2 plays an important physiological role, practically in all the organs and systems. Also, ACE2 exerts protective functions in various models of pathologies with acute and chronic inflammation. While ACE2 downregulation by SARS-CoV-2 spike protein leads to an overactivation of Angiotensin (Ang) II/AT1R axis and the deleterious effects of Ang II may explain the multiorgan dysfunction seen in patients. Specifically, the role of Ang II leading to the appearance of Macrophage Activation Syndrome (MAS) and the cytokine storm in COVID-19 is discussed below. In this review, we summarized the latest research progress in the strategies of treatments that mainly focus on reducing the Ang II-induced deleterious effects rather than attenuating the virus replication.

## 1. Introduction

As of early April, the death toll of Coronavirus Disease 2019 (COVID-19) pandemic caused by a coronavirus SARS-CoV-2 exceeds thousands of people. Angiotensin-Converting Enzyme 2 (ACE2) that is recognized as a protective molecule against kidney, heart, liver, and respiratory diseases [1] in the context of negative regulation of the Renin-Angiotensin System (RAS), is now also recognized as a functional receptor for SARS-CoV-2 [2,3]. The virus-ACE2 recognition is too efficient and the SARS-CoV-2 spike protein has a strong binding affinity to human ACE2 [4,5]. This virus uses ACE2 not only for its cellular entry to the host cell but also downregulates ACE2 expression [6,7], contributing to the pathogenesis of the severe acute respiratory distress syndrome (ARDS) or severe acute respiratory syndrome (SARS), see Fig. 1 [8]. The epidemiologic data suggests that there is an elevated level of ACE2 expression in young adults as compared to aged groups [9]. The less ACE2 content in aged groups may contribute to the pre-dominance of complications in aging.

The RAS system includes angiotensinogen (ANG), angiotensin (Ang) I, Ang II, renin, and the Angiotensin-Converting Enzyme (ACE). The substrate ANG is degraded to inactive Ang I by the enzyme renin, which is then cleaved by ACE to generate an octapeptide Ang II [10]. The

ACE2, a recently identified member of RAS is an 805 amino-acid type-I transmembrane protein that degrades Ang II to Ang-(1-7) [11], see Fig. 1. The two isoforms of Ang II receptors that belong to the G-protein coupled receptor superfamily, Ang II type 1 receptor (AT1R) and Ang II type 2 receptor (AT2R) have been identified [12]. Ang II exerts its biological functions mainly through the AT1R [13], but in some harmful pathological conditions, Ang II/AT1R is overactive, see Fig. 2 [10]. Also, Ang II may be implicated in the impairment of nitric oxide bioavailability, cell oxidative stress, and increases the retention of sodium and water by the release of aldosterone and vasopressin, see Fig. 2 [14]. ACE2 counteracts the deleterious effect of Ang II by maintaining the balance between the two axes ACE2/Ang-(1-7)/Mas receptor and ACE/Ang II/AT1R of the RAS. Thereby, reducing the bioavailability of Ang II and increasing Ang-(1-7) expression [15].

ACE2 also limits the macrophage expression of several pro-inflammatory cytokines in vitro, including Tumor Necrosis Factor (TNF- $\alpha$ ) and Interleukin-6 (IL-6) [16]. But in the case of COVID-19, this virus tends to downregulate ACE2 thus enhancing macrophage expression [17], as observed in the Macrophage Activation Syndrome (MAS), see Fig. 1. Severe SARS-CoV-2 patients show similar symptoms than MAS patients like persistent fever, multiple organ failure, and the same sustained cytokine pattern [18]. ACE2 is abundantly expressed in the

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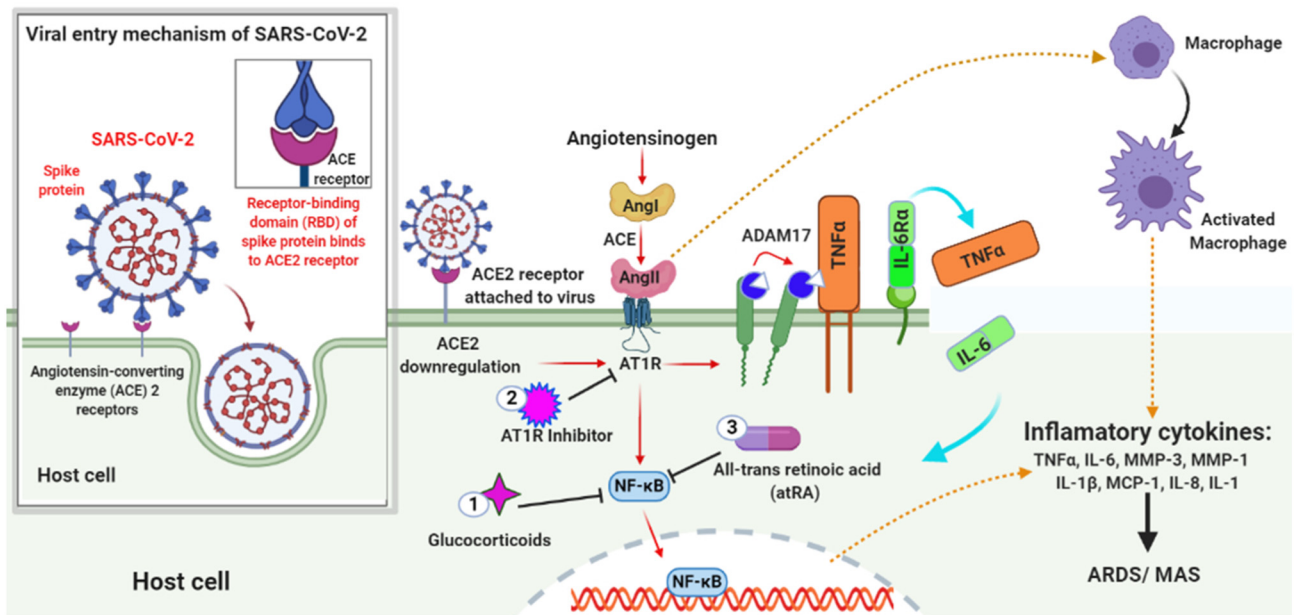


Fig. 1. Illustration of ACE2 Downregulation in COVID-19 patient and appearance of MAS. The virus enters the host cell by interacting with the ACE2 receptor through its spike protein. Later, the virus downregulates the ACE2 expression that in turn upregulates Ang II. Ang II is a product of the RAS system obtained by the cleavage of Ang I by enzyme ACE. The upregulated Ang II interacts with its receptor AT1R and modulates the gene expression of several inflammatory cytokines via NF-κB signaling. This Ang II/AT1R interaction also influences the macrophage activation that in turn produces the inflammatory cytokines thereby, inducing ARDS or MAS. Also, some metalloproteases like ADAM17 shed these proinflammatory cytokines and ACE2 receptors to the soluble form which aids in loss of the protective function of surface ACE2 and may increase SARS pathogenesis. The treatment with Glucocorticoids, AT1R inhibitor, and All-trans retinoic acid tends to inhibit NF-κB signaling thus reducing the cytokine storms thereby improving the severity of SARS-CoV2 infection.

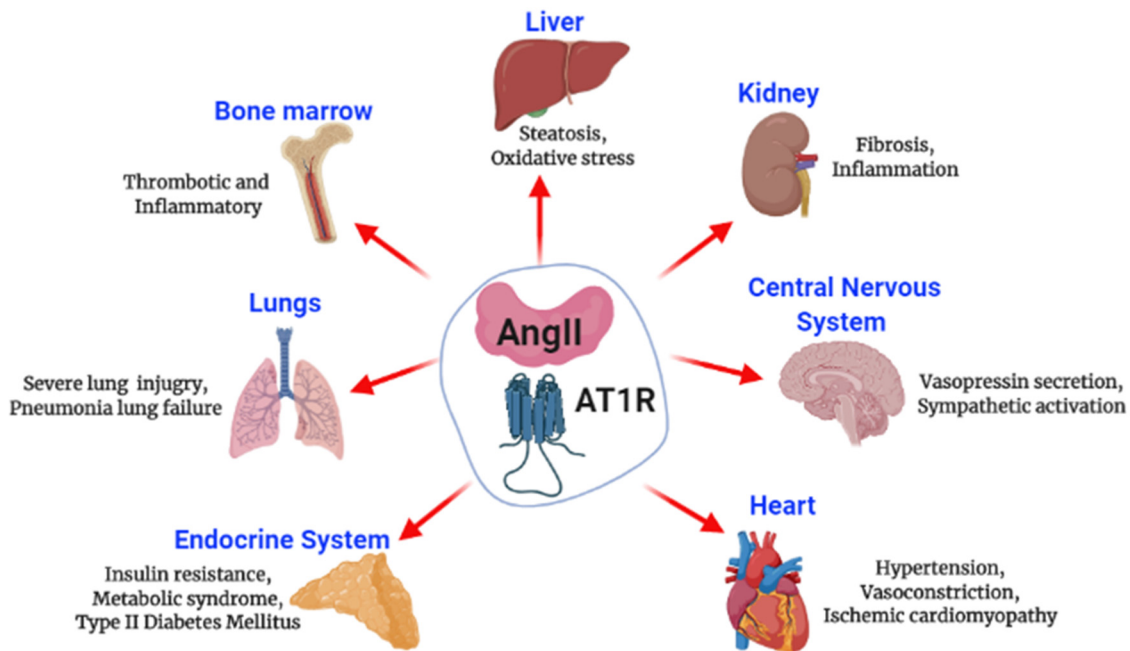


Fig. 2. Schematic representation of Angiotensin II effects. The interaction of Ang II with AT1R mediates the harmful effects leading to multi-organ failure.

luminal surface of tubular epithelial cells in the kidney [19], and cardiomyocytes in the heart [20]. Some level of ACE2 is also seen in the gut and lungs [21]. This wide distribution pattern of ACE2 expression explains the multiple organ dysfunction with COVID-19 and MAS patients. Thus, we hypothesized that the infection with SARS-CoV-2 may lead to MAS through the downregulation of ACE2 and the involvement of Ang II.

protective role of ACE2 in different organs and the deleterious effect caused by the downregulation of ACE2 in SARS-CoV-2 infection and MAS. Based on this discussion we have also suggested possible treatments for the better outcome of severe COVID-19 patients.

Regarding the above, in this review, we have discussed the

## 2. Protective role of ACE2 in different organs and system

### 2.1. ACE2 in different settings of pathologies in the lungs

It has been demonstrated the capacity for local Ang II generation within the parenchyma of the lungs [22]. After an acute injury, the expression of AGT mRNA, AGT protein, and the Ang II derived from it had increased [23]. Ang II is known to be proapoptotic for epithelial cells including the lung [24] and significant *in vivo* evidence suggests that Ang II plays a very important role in lung inflammation and fibrogenesis [25]. Thus, blocking Ang II synthesis or its functions ameliorates lung damage. In contrast, ACE2 has been positively correlated with the differentiation state of epithelia [26]. The abundant expression of ACE2 is seen in differentiated cells than in the undifferentiated cells [27]. In the respiratory tract, ACE2 is predominantly expressed in the alveolar and bronchiolar epithelium, endothelium, and smooth muscle cells of pulmonary vessels [26]. The state of cell differentiation and ACE2 expression levels are important determinants of the susceptibility of human airway epithelia to infection [28]. Kuba et al. discovered that the injection of the SARS-CoV Spike protein could decrease the expression of ACE2 in the lungs and cause acute lung injury [29].

Animal models prove ACE2 protective effects in the different settings of infections and no infections pathologies of the lungs [7,8,29–31]. In mice, ACE2 protects against acute lung injury triggered by acid aspiration and sepsis [29]. In this model which mimics human acute lung injury, the loss of ACE2 resulted in worsened oxygenation, massive lung edema, and increased inflammatory cell infiltration [29]. Similarly in Bleomycin-induced lung injury, ACE2 knockout mice exhibited poorer exercise capacity, worse lung function, and exacerbated lung inflammation and fibrosis compared with age-matched wild-type [32]. The genetic inactivation of ACE2 causes severe lung injury in H5N1-challenged mice [31].

A soluble and catalytically active form of ACE2 has also been described in the lung [26]. ACE2 is released from the surface of epithelia into the airway surface liquid via cleavage by TACE (ADAM17) and other sheddases [33,34]. In response to stimuli, many membrane proteins undergo either shedding or internalization [33] Haga et al. reported that the SARS-CoV Spike protein once binds to ACE2, induces ACE2 shedding by further activating cellular ADAM17 [35,36]. While some authors suggested that increasing soluble ACE2 may be a negative feedback mechanism to control viral infection [26,33], enhanced ACE2 shedding resulting from RAS overactivation, and subsequent ADAM17 upregulation drives pathogenesis in several models of cardiovascular diseases [37,38]. Ang II accumulation by the loss of membrane ACE2, also activates ADAM17, creating a vicious circle of membrane shedding of ACE2, RAS overactivation, and inflammation [39].

In the respiratory system, the administration of recombinant ACE2 has been shown to have a beneficial effect on improving lung pathologies and patient's survival rate in ARDS and SARS induced by viruses [30,40,41]. Importantly, the depletion of ACE2 at the cell surface with a loss of ACE2-mediated tissue protection is a critical pathological outcome of SARS-CoV-2 infection. As ACE2 also has nuclear effects [42,43], the efficacy of the recombinant human ACE2 administration in patients with COVID-19 will require careful experimentation in appropriate models together with well-controlled clinical trials. For example, ACE2 regulates alveolar epithelial cell's survival by inhibiting both JNK phosphorylation and apoptosis [44]. On the other hand, the use of ACE inhibitors or AT1R-selective antagonists exerted inhibitory effects on bleomycin-,  $\gamma$  irradiation-, amiodarone- and paraquat-induced pulmonary damage in rats, and hyperoxia-induced chronic lung disease in neonatal rats [45–48].

Moreover, the lung epithelial stem/progenitor cell express ACE2 [49]. A subset of putative stem/progenitor cells has been reported as the major target for SARS coronavirus in the human lung [28,50]. The effects of the infection of these cells may result in cell death, infiltration of the immune cells, including macrophages and the production of

proinflammatory cytokines. Recently, an antitrypanosomal drug that enhances the enzymatic activity of ACE2 improved the angiogenic progenitor cell functions in the lung [51]. The exogenous administration of ACE2 could induce MSCs proliferation and differentiation and participate in healing injured lung from inflammatory lung disease [26,52]. Thus, the downregulation of ACE2 during SARS-CoV-2 infection decreases the lung's ability to recover from the acute injury and may cause severe pneumonia lung failure, as clinically observed, see Fig. 2.

### 2.2. ACE2 protects the liver from acute and chronic inflammation

Normal liver tissue expresses a low amount of ACE2 [53] but in the case of a liver injury, ACE2 is upregulated at the gene and protein level, accompanied by an increase in ACE2 activity, possibly in response to increasing hepatocellular hypoxia [54]. In a chronic liver injury model, the loss of ACE2 activity worsens liver fibrosis [55] and liver steatosis [56]. In Multiple Drug-Resistant Gene 2-Knockout Mice, ACE2 therapy was seen to inhibit the Chronic Biliary Fibrosis [57]. ACE2 mice knockout study demonstrated that the marker genes for oxidative stress signaling (Gpx1, catalase, and SOD2) and pro-inflammatory cytokines like TNF- $\alpha$ , monocyte chemotactic protein-1 (MCP-1) and Interleukin-8 (IL-8) were significantly increased resulting in aggravation of oxidative stress and inflammation in the liver, see Fig. 2 [56]. ACE2/Ang-(1–7)/Mas axis acts through the Akt/PI3K/IRS-1/JNK insulin signaling pathway leading to improved liver insulin resistance [58]. All these researches suggest that ACE2 may play a role in liver disease pathogenesis.

### 2.3. ACE2 is physiologically renoprotective

In humans, kidneys exhibit ACE and ACE2 colocalization in apical brush borders of the proximal tubules and glomeruli [59]. In renal endothelial cells, Ang II can increase TNF- $\alpha$  expression and produce kidney injury in immune-complex nephritis, lupus nephritis, anti-glomerular basement membrane, and puromycin nephrosis [60]. TNF- $\alpha$  from endothelial cells also has paracrine effects in target cells on the endothelial surface and other neighboring cells [60]. Also, different *in vitro* and *in vivo* models have been shown that Ang II increases IL-6, Transforming Growth Factor Beta (TGF- $\beta$ ), connective tissue growth factor (CTGF), parathyroid hormone-related protein (PTHrP) and other growth factors [61,62]. Several chemokines induced by Ang II have been associated with the high inflammatory cell recruitment observed in renal pathologies, see Fig. 2 [63–66]. In contrast, ACE2 protects against inflammation and fibrosis by limiting the induction of renal TGF- $\beta$  expression [64]. Thus, counteracting the ACE action and protects the renal system [65].

### 2.4. ACE2 in cardiovascular function

ACE2 is widely distributed in cardiovascular tissue and various cellular compartments including the coronary microcirculation, cardiomyocytes, and cardiomyocytes [66]. The upregulation of ACE2 is seen in the case of heart failure and ischemic cardiomyopathy [67] where it depends on Ang II as the substrate for Ang-(1–7) generation [68]. The deletion of the ACE2 gene in mice resulted in abnormal heart function [69,70], increased Ang II levels, upregulation of hypoxia-induced gene, leading to severe cardiac contractility defect [71]. Also, ACE2 negatively regulates RAS to control blood pressure [71] and confers endothelial protection [72]. Moreover, ACE2 tends to diminishes Ang II-induced oxidative stress and inflammation through AT1R downstream phosphatidylinositol-3-kinase (PI3K) signaling [73]. Overexpression of ACE2 protects the heart against myocardial injuries induced by Ang II infusion in rats [74]. The vascular endothelial dysfunction observed in aortic rings from rats with myocardial infarction was also reversed by the chronic infusion of Ang-(1–7) [75]. Relatively,

a study revealed that ACE2 shedding contributes to the development of neurogenic hypertension [76]. Suggesting that ACE2 is an essential regulator of heart function.

### 2.5. ACE2 in the central nervous system

ACE2 tends to be localized in the cytoplasm of neuronal cells in the brain where its expression is involved in the control of cardiovascular function [77]. ACE2/Ang-(1-7)/Mas exerts neuroprotective functions in endothelin-1-induced ischaemic stroke in rodent models [78]. Moreover, an *in vivo* study with Mas receptor deficiency showed an increase in the macrophage infiltration and proinflammatory genes expression in the spleen and spinal cord, worsening the experimental course of autoimmune encephalomyelitis [79]. ACE2 tends to drive neoantigen-specific immune responses by effecting dendritic cell function to enhance their ability to induce FoxP3<sup>+</sup> and IL-17A<sup>+</sup> effector T cell thereby, controlling the immune response [80]. Furthermore, ACE2 overexpression in the brain attenuates neurogenic hypertension by inhibiting cyclooxygenase mediated inflammation [81,82]. Some research also proved that ACE2 mediates the reduction of oxidative stress in the brain and improve the autonomic function [83]. Besides, ACE may be detrimental to Alzheimer's disease and the use of an AT1R inhibitor ameliorates the cognitive impairment thus showing a beneficial effect on Alzheimer's disease [15,84].

### 2.6. ACE2 in intestinal immunity

ACE2 regulates intestinal epithelial immunity by controlling amino acid homeostasis, prevents the alteration of antimicrobial peptide expression, and maintains the ecology of the gut microbiome [85]. ACE2 expression in colonic epithelial cells is positively associated with Natural Killer (NK) cells and T cell-mediated cytotoxicity along with type I immunity and negatively associated with phagocytosis and complement activation [86]. In ACE2 knockout mice, Dextran Sodium Sulphate (DSS) and Trinitrobenzene Sulphonic Acid (TNBS)-induced colitis challenges resulted in infiltration of inflammatory cells, significant shortening of the colon length, intestinal bleeding, crypt damage, weight loss, and severe diarrhea [87]. Also, ACE2 is a key regulator of dietary amino acid homeostasis in colitis [85]. Amino acids and nicotinamide can activate the mammalian target of rapamycin (mTOR), which is involved in cell proliferation, survival, redox sensor, longevity, and cellular senescence, protein synthesis and transcription [85]. The deficiency of ACE2 causes a critical impairment of nicotinamide and tryptophan which increases the susceptibility to intestinal inflammation and decreases the regenerative responses [85,88].

### 2.7. ACE2 in the endocrine system

Recent evidence suggests that enhanced circulating levels of Ang II are involved in the development of insulin resistance, type 2 Diabetes Mellitus (DM), and metabolic syndrome, see Fig. 2 [89,90]. In a rat model of DM, the expressions of ACE2, Mas receptor, and Ang-(1-7) levels in enterocytes are considerably higher compared with controls, and Ang-(1-7) decreased the glucose uptake [91]. Moreover, the evidence showed that ACE2 can attenuate fibrosis, increase islet insulin content, and stimulate beta-cell proliferation in the pancreas probably by increasing the intracellular calcium influx and restored impaired mitochondrial oxidation [92]. The involvement of Ang II/AT1R signaling leads to cell apoptosis and ROS generation due to hyperglycemia [93].

A high grade of inflammation is also important in DM pathogenesis. Ang II-induced CXCL16 endothelial expression is through the AT1R and RhoA/p38-MAPK/NF- $\kappa$ B activation [94]. Ang II activates the Rho/Rho-associated protein kinase (ROCK) pathway more than in NF- $\kappa$ B activation and subsequent IL-6 expression [95]. The circulating CXCR6-expressing platelets, neutrophil, monocyte, and CD8T lymphocytes are

elevated in patients with metabolic syndrome [94]. Interestingly, the AT1R blockade improved the CXCL16 angiogenic properties and decreased the monocyte and lymphocyte cellularity along with its activation [94]. Thus, the downregulation of ACE2 may have important metabolic repercussions in patients who suffered from DM and SARS-CoV-2 and may explain why these patients are more susceptible to develop complications.

### 2.8. Role of ACE2 in bone marrow

Transcriptomic molecular studies demonstrated that the hematopoietic bone marrow (BM) stromal niche contains local RAS, AT1R, AT2R, and the inhibitory natural stem cell regulator tetrapeptide N-Acetyl-Ser-Asp-Lys-Pro (AcSDKP) [96]. Many biological functions like proliferation, migration, angiogenesis, and fibrosis in BM cells are mediated by RAS [97]. ACE is a regulator of hematopoiesis, especially, the role of Ang II in the proliferation of all lineages in BM has been extensively proven [98]. Ang II/AT1R is also involved in Myeloid differentiation and development. Importantly, neutrophils level decreased by more than 30% in ACE-knockout mice [99]. Also, acute ACE inhibition showed an increase in the AcSDKP level in plasma [100] AcSDKP substantially inhibits cell cycle entry of normal hematopoietic stem cells (HSCs) and protects hemopoiesis against damage caused by cycle-active cytotoxic agents [101] AcSDKP can also inhibit the proliferation of lymphocytes, stimulate angiogenesis and have antifibrotic effects *in vivo* [15].

Ang II Receptor-Associated Protein amplifies the thrombopoietin receptor Mpl which is involved in megakaryocyte growth and thrombocyte development, controls the hematopoietic stem cells homeostasis and self-renewal [102]. Ang II/AT1R induce platelet activation and production indicators developing more thrombotic and inflammatory effects, see Fig. 2 [103]. Studies demonstrated that Ang II increases rolling thrombocytes, adhered thrombocytes on the leukocytes and the endothelial cells, rolling leukocytes, and adhered leukocytes, as well as an escalation in thrombocyte-leukocyte-endothelial cell relations [98,103]. Therefore, in pathological conditions, Ang II/AT1R over-activation may lead to thrombotic complications.

Ang II was found to control the CD115 in HSCs. CD115 influences the differentiation and function of macrophage [104]. Ang II also controls monocytic cells over BM stromal cell-derived TNF- $\alpha$  to increase macrophage colony-stimulating factor (M-CSF)-induced management of monocytic cells [98,105]. Similar to these findings, another study demonstrated that the deficiency of ACE2 in BM-Derived Cells increases the expression of TNF- $\alpha$  in Adipose Stromal Cells [106]. It suggested that ACE2 expression in BM cells control the inflammation in adipose tissue. ACE2 deficiency in BM-derived cells also promotes atherosclerosis through the regulation of Ang II/Ang-(1-7) peptides, [107].

## 3. An excessive inflammatory response is deleterious: Macrophage Activation Syndrome

MAS or secondary Hemophagocytic lymphohistiocytosis (HLH) is a poorly recognized syndrome characterized by a fulminant cytokine storm, multiple organ dysfunction, and a high mortality rate [108]. MAS can occur during an autoimmune, tumor, and even an infectious disease [109,110]. Viral infections have especially been linked to this syndrome in adults [111,112]. An inappropriate immune stimulation and a self-perpetuating excessive inflammatory response are key facts within the pathogenesis of MAS [110,113], and the over-activation of tissue macrophages for the release of a storm of cytokines is a dominant feature observed both in MAS and severe COVID-19 patients [114-117].

Persistent fever is the most common clinical manifestation seen in MAS [118]. Hepatobiliary dysfunction with hepatosplenomegaly, fibrinolytic consumptive coagulopathy, hyperferritinemia, and hemophagocytosis in the BM, are other common clinical and laboratory

features [119]. Neurological dysfunction and acute kidney injury may also be present and could be considered as poor prognostic indicators [120,121]. The early detection of MAS with the laboratory tests including soluble interleukin 2 receptor alpha chain (sCD25) and soluble CD163 (sCD163) [122] has a profound impact on a patient's outcome.

#### 4. Downregulation of ACE2 in COVID-19 and MAS

A direct link between ACE2 in the progression of MAS and COVID-19 has not been described yet. However, the excess of Ang II associated with ACE2 dysregulation in COVID-19 [123] leading to the cytokine storm, also seen in MAS [119] could explain the appearance of MAS in the course of SARS-CoV-2 viral infection, see Fig. 1. The rationale for this concept stems from the following evidence: (1) we have previously described how the overexpression of Ang II exert deleterious effects in almost all organs and system. Ang II is a well-established pro-inflammatory peptide that closely interacts with the immune system and can modulate the regional cytokine milieu [124–127]. (2) Macrophages expressed almost all components of the RAS system [23,128,129]. (3) Furthermore, the monocyte mediated inflammation is directed by Ang II-induced cytoskeleton rearrangement and monocyte migration to the inflammation site [130,131]. (4) Macrophage maturation and differentiation also require Ang II/AT1R signaling [128]. (5) Ang II plays a role in macrophage function *per se* and the neighboring cells through autocrine/paracrine mechanisms [23,131,132]. (6) An excessive inflammatory response by the over-activation of tissue macrophages is involved both in MAS [110,113] and severe COVID-19 patients [114–117]. The regulation of these cytokines along with monocyte/macrophage with Ang II is discussed below. Also, the role of the metallopeptidase domain 17 (ADAM17) in Ang II-macrophage inflammation will be analyzed.

The increased oxidative stress, inflammation, and apoptosis seem to be a common mechanism of Ang II worsening the course of several inflammatory diseases [69,79,133]. In COVID-19 patients, the increased serum levels of several cytokines and chemokines have been associated with the disease severity and death [134–137]. *In vitro* studies showed the involvement of macrophages, T cells, NK cells proliferation [138], dendritic cell migration, CCR7 expression in Ang II-induced renal damage [139]. Ang II also triggers vascular damage via AT1R by upregulating the connective tissue growth factor (CTGF), a mediator of TGF- $\beta$  [140], inducing adhesion molecules, recruiting inflammatory cells, and modulating the IL-1 $\beta$ , IL-18, IFN $\gamma$ , TNF- $\alpha$ , and IL-6 cytokine expression [60,63,119,141], see Fig. 1. The TNF- $\alpha$  induces macrophage polarization toward the M1 phenotype creating a vicious circle [142]. Although TNF- $\alpha$  is produced by various cell types, the primary source of this cytokine is monocytes/macrophages [143], and in these cells, Ang II upregulates IL-6 and TNF- $\alpha$  gene expression being NF- $\kappa$ B the potential mediator of these Ang II-induced inflammatory process [63,144,145]. Moreover, TNF- $\alpha$  and IFN $\gamma$  induce the expression of CXCL16 on dendritic cells, B cells, and macrophages [146,147]. Thus, in both the cases with MAS and COVID-19, Ang II may initiate events leading to innate and acquired immune response.

It has been described that a pool of monocytes resides in clusters of ~50 cells in the resting spleen [124,130]. Upon Ang II-AT1R interaction, splenic monocytes increase their motility and intravasate into nearby splenic veins [124]. But in such cases, ACE2 activity is increased suggesting their protective role during inflammation [148]. In mice, this “emergency reservoir” releases up to 1 million monocytes within 24 h after myocardial infarction, which is subsequently recruited into the infarct mainly via interaction of the chemokine MCP-1 with its cognate receptor CCR2 [130,149]. Ang II can promote CCL2 generation and release, inducing mononuclear leukocyte interactions with the endothelium [150]. Corroborating to the above, CCL2, the most potent chemokines at recruitment of CCR2 monocytes were seen to be upregulated in the bronchoalveolar fluid in severe COVID-19 patients [151]. Besides, Ang II increases the production of IL-8, Fractalkine, RANTES,

and IP-10, among other chemotactic factors [63,152–154], and promotes CXCL16 endothelial expression through AT1R via RhoA/p38-MAPK/NF $\kappa$ B activation [94,155].

In animal models that are characterized by macrophage-mediated inflammation, the deletion of the receptor Mas enhances the migratory capacity of macrophages and induces the M1 phenotype [79]. Similar results have been reported with the specific deletion of ACE2 [156]. Mas deficiency especially affects CD11b+ macrophages interfering with the cytokine expression and activation capacities of different macrophage subtypes and may drive proinflammatory M(LPS + IFN $\gamma$ )-like responses [79]. ACE inhibitors or AT1R antagonists can modulate cellular adhesion and chemotaxis [131,157–159]. For example, the blockade of AT1R improve CXCL16 angiogenic properties and decreased the monocyte and lymphocyte cellularity and activation [94]. In addition to CXCL16, The beneficial effects of a selective AT2R agonist were associated with the decreased recruitment or infiltration of macrophages in the lungs, reduced lung inflammation [160], diminished pulmonary collagen accumulation and improved cardiopulmonary complications through the downregulation of CCL2, IL-6, and TLR4 [161].

Macrophage maturation also requires Ang II/AT1R signaling. Ang II controls the c-Fms in HSCs and monocytic cells over local TNF- $\alpha$  to increase M-CSF-induced management of monocytic cells [124]. During the process, monocytes expressed the whole components for Ang II generation and increased the production of Ang II [162]. Moreover, T lymphocytes contain a functional NADPH oxidase and an AT1R [163]. Ang II via NADPH oxidases stimulates T cell proliferation and activates it to produce TNF- $\alpha$ , IFN $\gamma$ , and TH1 generation [164]. Thus, ACE2/Mas deficiency affects macrophage phenotypes and functions and leads to an increase in oxidative stress and impaired endothelial function [79].

Evidence is accumulating that ADAM17 is an important regulator of the acute inflammatory response [165–169]. In addition to ACE2, it is a primary shedder of relevant inflammatory factors, including TNF- $\alpha$ , its two receptors TNFR-I (CD120a) and TNFR-II(CD120b), IL-6R, ligands of ErbB (e.g. TGF $\alpha$  and amphiregulin), and the L-selectin (CD62L) and ICAM-1 adhesion molecules [170–172]. ADAM17 also regulates leukocyte rolling along activated endothelium and leukocyte transmigration by shedding L-selectin, CX3CL1, ICAM-1, and VCAM-1 as well as JAM-A [173,174]. Macrophage ADAM17 is an essential component for activation and the pro-inflammatory phenotype [175–178]. Interestingly, the relationship between Ang II and ADAM17 pathogenic effects has been well studied [34,179–181]. Ang II-mediated proteolytic loss of ACE2 is associated with elevated ADAM17 activity prevented by AT1R blockade [39], while Ang-(1–7)/Mas signaling inhibits LPS-induced alveolar epithelial cell apoptosis by inhibiting LPS-induced shedding activity of ADAM17 [182]. Loss of ADAM17 suppressed Ang II-mediated migration and proliferation in VSMCs [183]. AT1R, promotes ADAM17-mediated ACE2 shedding in the brain of hypertensive patients, leading to a loss in compensatory activity during neurogenic hypertension [184].

#### 5. Immune suppression therapy reduces Ang II-dependent inflammation and MAS

The above discussion suggests that the decrease of ACE2 is a major factor contributing to the pathogenesis of a variety of pathologies in the course of chronic or acute inflammation by permitting Ang II accumulation. In COVID-19 patients appeared to have elevated levels of plasma Ang II, which were in turn correlated with total viral load and degree of lung injury [185]. Accordingly, therapies aimed at increasing ACE2 expression might attenuate inflammation and can be used as a novel therapeutic tool. Since the downregulation of ACE2 appears to be a shared phenomenon in ARDS during viral or bacterial infection [7,24,25,29,32,186], the administration of the recombinant ACE2 or AT1R blockers can ameliorate coronavirus SARS-CoV-2 lung complications as well as have been reported for syncytial virus and H5N1 virus

infection-induced lung injury [30,31,40].

AT1R blockers are among the most common medications used for the treatment of cardiovascular diseases with a high-security profile [187]. As mentioned earlier, in adults AT1R is expressed in cells of the immune system and in particular on macrophages, T, and B lymphocytes [141,162]. Ang II exerts pro-inflammatory responses mostly binding to AT1R [188–191], and the treatment with one AT1R blocker efficiently prevented Ang II-inducing inflammation [192–195]. AT1R inhibitors suppressed the expression of Ang II, IL6, and directly blocked AT1R, thus avoiding STAT3 activation [196]. Additionally, they suppress TNF- $\alpha$  synthesis *in vitro* and *in vivo*, see Fig. 1 [197] and are associated with a lower level of plasma TNF- $\alpha$  [198]. AT1R blockade produces a significant decrease in IFN- $\gamma$  producing peripheral blood lymphocytes both a protein and IFN- $\gamma$  mRNA levels [199]. Moreover, AT1R blockade attenuated end-organ damage [200].

Accumulating evidence suggests that AT1R inhibitors have potent anti-inflammatory actions not usually associated with the activation of the RAS system [201–205]. These drugs also can exhibit antioxidant effects [205–207]. Candesartan suppressed TNF-induced chemokine expression and NF- $\kappa$ B activation, decreased reactive oxygen generation, and reinstated redox homeostasis [208]. redox-sensitive NF- $\kappa$ B-mediated inflammation has been described. The same drug diminished the TLR signaling pathway and the downstream effectors TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and NF- $\kappa$ B [203]. Amelioration of renal tissue inflammation with AT1R blockade was associated with a significant reduction of MCP-1 [189]. The peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ) also is involved in the anti-inflammatory effects of AT1R antagonists [204,209,210]. Importantly, a study demonstrated that the treatment with one AT1R inhibitor induced the expression of FoxP3 in CD4+CD25+ T cells [211]. Therefore, the AT1R inhibitor administration has a profound impact on the immune response and the inhibition of monocyte mobilization from their reservoirs represents a powerful anti-inflammatory action that may have therapeutic implications [212].

With regards to the activation of pulmonary RAS influencing the pathogenesis of ARDS and SARS, three reports recommended the use of AT1R inhibitor or blocker to improve the quality of life and survival outcomes [213–215]. The chronic AT1R blockade also results in ACE2 upregulation in both animal models and humans [216–221]. Unless ACE, ACE2 activity is unaffected by these drugs [222]. The AT1R blocker has been suggested by some researchers and reported to ameliorate coronavirus SARS-CoV-2 lung complications [7,223,224]. Human recombinant ACE2 also is a negative regulator of Ang II-induced deleterious effects [225–227]. It increased Ang 1–7 while lowered Ang II levels and reduced NADPH oxidase activity [228]. ACE2 administration also suppresses pulmonary arterial pressure and resistance improving lung compliance during acute hypoxia [229]. Moreover, the administration of recombinant ACE2 was well tolerated by healthy human subjects [41]. The neutralization of the 2019 novel coronavirus by the administration of ACE2 protein has been proposed as a therapeutic modality [230,231]. Recombinant ACE2 also remarkably rescued Ang II-induced hypertension, pathological hypertrophy, oxidant injury, and cardiac dysfunction [232,233]. Nevertheless, the efficacy of the recombinant ACE2 protein or AT1R blockers on lung diseases should be further tested in clinical settings.

One additional potential strategy for COVID-19 could be to suppress the rate of cleavage of ACE2 from the surface of lung epithelial cells leading to retention of the enzymatic activity and reduced Ang II. The evidence also suggests that the disruption of ADAM17 expression by siRNA reduces the ACE2 shedding [34]. Furthermore, ongoing research suggests that ADAM17 inhibitors had efficacy in some inflammatory conditions [234–236]. Preclinical trials using inhibitors of ADAM17 showed effectivity in mouse models of arthritis [237,238]. Such strategies in COVID-19 would need to account for the fact that ACE2 is cleaved at more than one site and that multiple enzymes appear to serve as sheddases in this process [225]. In addition, ADAM17 is involved in

the regulation of multiple cellular processes, both pathological and normal [239–241]. Therefore, one of the biggest challenges in developing agents inhibiting ADAM17 is to attain selective inhibition of pathological processes or ACE2 shedding while sparing normal processes to avoid adverse effects. A member of the rhomboid family, iRhom2 is predominantly expressed in immune cells and iRhom2 is needed for transport of ADAM17 to the cell surface [242–244]. The inhibition of iRhom2 would lead to a selective deficiency of ADAM17 in immune cells with no effects on epithelia, representing a new perspective of ADAM17 blockade.

Similar to the AT1R blockade, the inhibition of NF- $\kappa$ B markedly attenuated the Ang II-induced inflammatory damage [245]. Upon infection, the role of Glucocorticoids (GCs) is to desensitize inflammation and to avoid an overshooting immune response, which may be detrimental for the organism. The GC's anti-inflammatory responses are in part, the result of interfering with the NF- $\kappa$ B signaling pathway, see Fig. 1 [246,247]. NF- $\kappa$ B signaling is essential for M1 macrophage polarization [248]. Thus, blocking such signaling can induce re-polarization from M1 to M2 [249]. Studies have demonstrated that Dexamethasone can reduce NF- $\kappa$ B activity [139], and can efficiently down-regulate the TNF- $\alpha$ -induced IL-1 $\beta$ , and NF- $\kappa$ B-driven transcriptional expression of matrix metalloproteinases like MMP-1 and MMP-3, TNF- $\alpha$ , IL-6, IL-8, IL-1 and MCP1 [250,251]. An increasing number of GCs receptor-induced genes are now recognized as contributing to the anti-inflammatory effects of GCs [252,253]. Moreover, the GCs target like airway epithelium engage in cross-talk with immune cells [254], then they act via the GCs receptor in airway epithelial cells to repress inflammatory responses [255]. Taking into account that Ang II upregulation may initiate events leading to innate and acquired immune response resulting in cytokine storm in both MAS and COVID-19 patients, the use of GCs could protect against Ang II-induced end-organ damage in both pathologies. Central management of MAS is its early recognition, followed by prompt treatment. Interestingly, the commonest initial treatment for MAS is also, corticosteroids [256]. Collectively, the above information incriminates the use of GCs as a valuable tool in patients complicated with SARS-CoV-2.

A problem to consider with the use of GCs would be whether they increase CoV-2 virulence. In several infectious conditions, including mononucleosis, pneumococcal pneumonia, tuberculosis, typhoid fever, tetanus, and pneumocystis pneumonia, GCs administration improved patients' survival [257]. Some studies demonstrated that the use of these drugs did not increase the viral yield in Herpes Simplex Virus type 1 [258,259], and HIV-1 [260]. Direct repression of HIV transcription by GCs have been described in various works [261,262]. Also, meta-analyses report lower reintubation rates in neonates, children, and adults that received corticosteroids despite the infectious disease [263,264]. Thus, we suggest that GCs are strong candidates as a therapeutic agent for limiting coronavirus SARS-CoV-2 inflammatory complications and death.

Mesenchymal stem cell (MSC)-based gene therapy is a novel therapeutic approach for several diseases that currently have limited treatment options [265,266]. Importantly, MSCs can also act as a vehicle for delivering a protective gene by overexpressing a transgene at the injured site also promoting local tissue repair [267]. ACE2/Mas receptor is expressed in MSCs and Ang-(1–7) supports migratory function and stimulates vascular repair-relevant functions [268]. In an animal model of acute lung injury (ALI) and ARDS induced by lipopolysaccharide (LPS), MSCs treatment significantly reduced LPS-induced pulmonary inflammation [266]. Furthermore, the administration of MSCs overexpressing ACE2 resulted in a further improvement in the inflammatory response and pulmonary endothelial function of LPS-induced ALI mice [267]. A recent *in vivo* study has demonstrated that MSCs can differentiate into lung epithelial cells [269,270]. Also, MSCs may also exhibit immunosuppressive properties [266]. A very recent study shown that the intravenous injection of MSCs significantly improved the inflammation situation and improves the outcome of

patients with COVID-19 pneumonia [271]. Thus, based on its anti-inflammatory and repair properties we suggest implicating the MSCs based treatment for COVID-19 patients.

Another promising therapeutic molecule could be All-trans retinoic acid (atRA), the active metabolite of Vitamin A. It has been described that All-trans retinoic acid (atRA) suppresses AT1R at both mRNA and protein levels [272,273]. Considering the above discussion about the involvement of Ang II/AT1R signaling in diabetes, atRA has proved to prevent the deleterious effects caused by hyperglycemia and Ang II [93]. As mentioned before about the NF- $\kappa$ B signaling, atRA tends to inhibit several inflammatory reactions by suppressing NF- $\kappa$ B-mediated gene expression of IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and MCP-1 *in vitro* and *in vivo* see Fig. 1 [273,274]. Furthermore, Retinoic acid protects cardiomyocytes from high glucose-induced apoptosis by inhibiting NF- $\kappa$ B signaling [275]. Thus, patients with DM may have an additional benefit with the use of this drug. Accordingly, the treatment with atRA showed an increase in gene and protein expressions of ACE2 in hypertensive rats [276]. All these results suggest that atRA could be an attractive candidate for the potential treatment of patients with coronavirus SARS-CoV-2.

The other drugs to be considered to treat SARS-CoV-2 infection would be the one that could modulate the levels of IL-1 and IL-6. Anakinra, a recombinant interleukin-1 (IL-1) receptor antagonist, has been used to treat a variety of autoinflammatory diseases [277]. Recently, a continuous intravenous Anakinra in a rapidly escalating dose regimen results in rapid serologic and clinical improvement in patients with MAS [278,279]. Moreover, the data from a phase 3 randomized controlled trial of Anakinra in sepsis, showed higher survival outcomes in patients with hyper-inflammation, without increased adverse events [280]. IL-6 antibody blocker and TNF- $\alpha$ -inhibiting agents have been reported to be effective in some MAS patients [281]. Tocilizumab is a recombinant humanized monoclonal antibody against the IL-6 receptor. Currently, a small sample clinical trial in China (ID: ChiCTR2000029765) has shown good efficacy in tocilizumab for SARS-CoV-2 [282].

## 6. Conclusion

ACE2 is a RAS component, widely distributed in almost all the organs. It plays a protective role mostly by counteracting the harmful effect of Ang II-induced inflammation. ACE2 being the receptor for SARS-CoV-2 and its wide distribution explains why some COVID-19 patients suffer from a variety of symptoms and potential complications. Ang II has important physiological effects in the immune response, particularly on the activation and the recruitment of monocytes/macrophages. Thus, the appearance of MAS during SARS-CoV-2 infection is an expected phenomenon that must be promptly identified and treated appropriately. We suggest strategies of treatments that mainly focus on reducing the Ang II-induced deleterious effects rather than attenuating virus replication. Thus, we aim that this review will contribute to the development of novel strategies to prevent and control the COVID-19 pandemic.

## Declaration of competing interest

The authors declare no competing financial interests.

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