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Review article

COVID-19 cytokine storm: The anger of inflammation

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ABSTRACT

Patients with COVID-19 who require ICU admission might have the cytokine storm. It is a state of out-of-control release of a variety of inflammatory cytokines. The molecular mechanism of the cytokine storm has not been explored extensively yet. The attachment of SARS-CoV-2 spike glycoprotein with angiotensin-converting enzyme 2 (ACE2), as its cellular receptor, triggers complex molecular events that leads to hyperinflammation. Four molecular axes that may be involved in SARS-CoV-2 driven inflammatory cytokine overproduction are addressed in this work. The virus-mediated down-regulation of ACE2 causes a burst of inflammatory cytokine release through dysregulation of the renin-angiotensin-aldosterone system (ACE/angiotensin II/AT1R axis), attenuation of Mas receptor (ACE2/MasR axis), increased activation of [des-Arg9]-bradykinin (ACE2/bradykinin B1R/DABK axis), and activation of the complement system including C5a and C5b-9 components. The molecular clarification of these axes will elucidate an array of therapeutic strategies to confront the cytokine storm in order to prevent and treat COVID-19 associated acute respiratory distress syndrome.

1. Introduction

The coronavirus infectious disease 2019 (COVID-19) that is spreading at the global scale is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an enveloped single-stranded RNA virus belonging to the Coronaviridae family, genus beta-coronavirus [1]. Non-structural proteins of this virus play a crucial role in virus replication while structural and auxiliary proteins are involved in morphogenesis and interfere with the host immunity response, respectively [2].

Accumulating evidence suggests that the host immunity response is contributing in severe forms of MERS-CoV, SARS-CoV and SARS-CoV-2 infections [3–5]. This immune response has been associated with a higher intensive care unit (ICU) admissions and mortality in COVID-19. In fact, higher concentrations of granulocyte-colony stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1alpha (MIP1A), and tumor necrosis factor alpha (TNFα) in comparison to non-ICU patients were reported in patients with COVID-19 [5]. In another study, higher levels of interleukin-2 (IL-2) receptor, interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), and TNFα were found in deceased patients with COVID-19 compared to patients who had recovered from the disease [6].

These immunologic reactions in severe COVID-19 may characterize the cytokine storm that is associated with untoward clinicopathological consequences. The cytokine storm is an out-of-control cytokine release that has been observed in some infectious and noninfectious diseases, leading to a hyperinflammation condition in the host (Fig. 1) [7]. This uncontrolled cytokine response might be accompanied with more immune cells activation including T helper 17 cell (Th17) differentiation from CD4+ lymphocytes. In fact, increased Th17 responses were reported in MERS-CoV, SARS-CoV and SARS-CoV-2 [8–11].

At least 10% of the patients with severe COVID-19 will eventually present lung injury, acute respiratory distress syndrome (ARDS) and involvement of multiple organs within 8–14 days of the onset of their illness [12]. These severe cases that develop respiratory failure show a series of pathological findings such as hyaline membrane formation, inflammatory infiltration with multinucleated syncytial cells in their lung pathology and a burst of cytokine release leading to morbidity and mortality [6,12].

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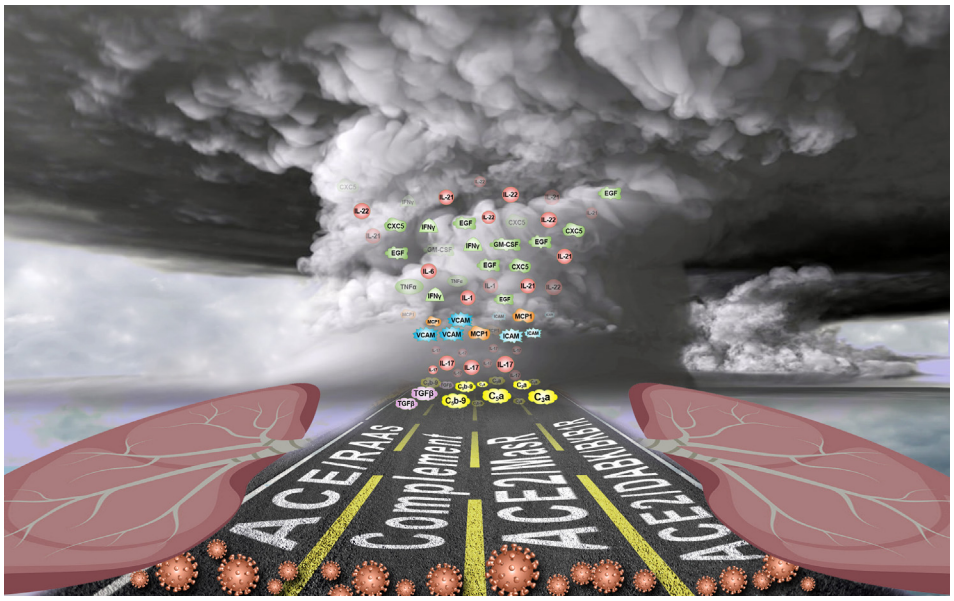

Fig. 1. SARS-CoV-2 driven ACE2 down-regulation leads to an array of complex and intertwined molecular interactions via at least four axes consisting of dysregulation of the ACE2/angiotensin II/AT1R axis, attenuation of ACE2/MasR axis, increased activation of ACE2/bradykinin B1R/DABK axis, and activation of the complement cascades, resulting to a tornado of inflammatory cytokine responses ,as described by Tisoncik et al. [7].

The initial cellular entry phase of the SARA-CoV-2 requires binding of its envelope homotrimeric spike glycoprotein to the membrane-bound form of angiotensin-converting enzyme 2 (ACE2) on the target cell [12,13]. The attachment of the virus with ACE2, as its cellular receptor, triggers internalization of the complex into the target cell, leading to the down-regulation of the ACE2 [14].

ACE2 internalization and its subsequent down-regulation would potentially result in unopposed function of angiotensin II (AngII) and decreased levels of angiotensin-(1–7) [14]. Since angiotensin-(1–7) has a key counter-regulatory role in many of the angiotensin type 1 receptor (AT1R)-related physiopathological functions, the SARA-CoV-2-mediated downregulation of ACE2 and the resulting increased overall ratio of Ang II to angiotensin-(1–7) leads to the deterioration of the pulmonary function and lung injury [13,15].

Therefore, the imbalance of ACE2/ACE levels in COVID-19 and the dysregulated angiotensin-II /AT1R axis of the renin-angiotensin-aldosterone system (RAAS) may partially be responsible for the cytokine storm and the resulting pulmonary damage [16,17]. The loss of the modulatory effect of angiotensin-(1–7) via its binding to the Mas receptor (MasR) that attenuates inflammatory response may be a further contributing factor to the hyper-inflammation status of severe cases of COVID-19.

Beyond ACE2 catalytic activity in RAAS and MasR-mediated actions, it has interesting effects on multiple molecular pathways which are involved in inflammatory response and cytokine release. However, potential cellular and molecular mechanisms of the cytokine storm in COVID-19 have not yet been explored extensively.

In this review, we specifically discuss the complex inflammatory molecular consequents of downregulation of ACE2 in the context of SARS-CoV-2, with a particular emphasis on the complement system and [des-Arg9]-BK or (DABK) in addition to ACE/ angiotensin-II/AT1R and ACE2/MasR axes. We propose a unifying molecular model to better understand the complex molecular events behind out-of-control cytokine response in severe COVID-19 patients. Undoubtedly, this insight will be pivotal to obtain a harmonized therapeutic strategy to confront this deadly viral infection and to protect the lungs during the cytokine storm.

2. ACE/Angiotensin II/AT1R axis

The renin-angiotensin-aldosterone system (RAAS), through its vasoactive peptides, regulates blood pressure, fluid volume, sodium and potassium balance. This elegant system also plays a significant role in the promotion and maintenance of inflammation [18].

It appears that activation of the RAAS system can induce inflammation in an independent mechanism of blood pressure through the AT1 receptor (AT1R) in the kidney and vasculature [19]. The secretion of profibrotic cytokines such as transforming growth factor beta (TFG-β) is stimulated during RAAS activation [20–22]. Furthermore, increased production of Ang II and activation of AT1R are accompanied with a pro-inflammatory response via activation of the complement cascade including C5a, C5b-9 [23]. This implies a cross-talk between RAAS and the complement system.

Ang II can activate the nuclear factor kappa B (NF-κB) pathway [24,25] via stimulation of the phosphorylation of the p65 subunit of NF-κB [26]. This will lead to increased production of IL-6 [27], TNFα, IL-1B and IL-10 [26]. After AT1R activation, Ang II regulates Mitogen-Activated Protein Kinases (MAPK) (ERK1/2, JNK, p38MAPK), which have important functions on cellular processes including the release of cytokines such as IL-1, IL-10, IL-12 and TNFα (Fig. 2) [28–30].

ACE2 enzyme is expressed in the heart, kidneys, testes, gastrointestinal tract and lungs [15,31]. It cleaves the Angiotensin I (Ang I) to generate the inactive Ang-(1–9) peptide, which can be changed to the vasodilatory peptide Ang-(1–7) by ACE or other peptidases. ACE2 can also directly metabolize Ang II to generate Ang-(1–7) [32].

SARS-CoV-2 uses ACE2 in type II pneumocytes of lung alveoli and club cells in bronchioles as the cellular entry receptor. Very recently, TMPRSS2 (as a major host protease), and ACE2 co-expression was reported among a subset of type II pneumocytes in the lung [31].

After the attachment of SARS-CoV-2 spike (S)-protein to ACE2, its intracellular binding site down-regulates ACE2. Consequently, following this down-regulation of ACE2, Ang II level increases in the serum leading to augmentation of the Ang II/AT1R axis activation, which is followed by *trans*-signaling of IL-6-sIL-6Ra complex, in which the gp 130-mediated activation of STAT3 occurs in the lungs' epithelial cells. Although SARS-CoV-2 itself activates NF-κB through pattern recognition receptors, it is the simultaneous activation of NF-κB and STAT3 that enhances NF-κB activation machinery (the IL-6 amplifier). This hyper-activation of NF-κB via the IL-6 Amp in the lungs induces a cytokine storm with subsequent ARDS that had been observed in severe COVID-19 patients [33,34].

Indeed, down-regulation of ACE2 which was accompanied with enhancement of Ang II levels in different types of lung injury triggered those pulmonary pathological changes that are commonly observed in

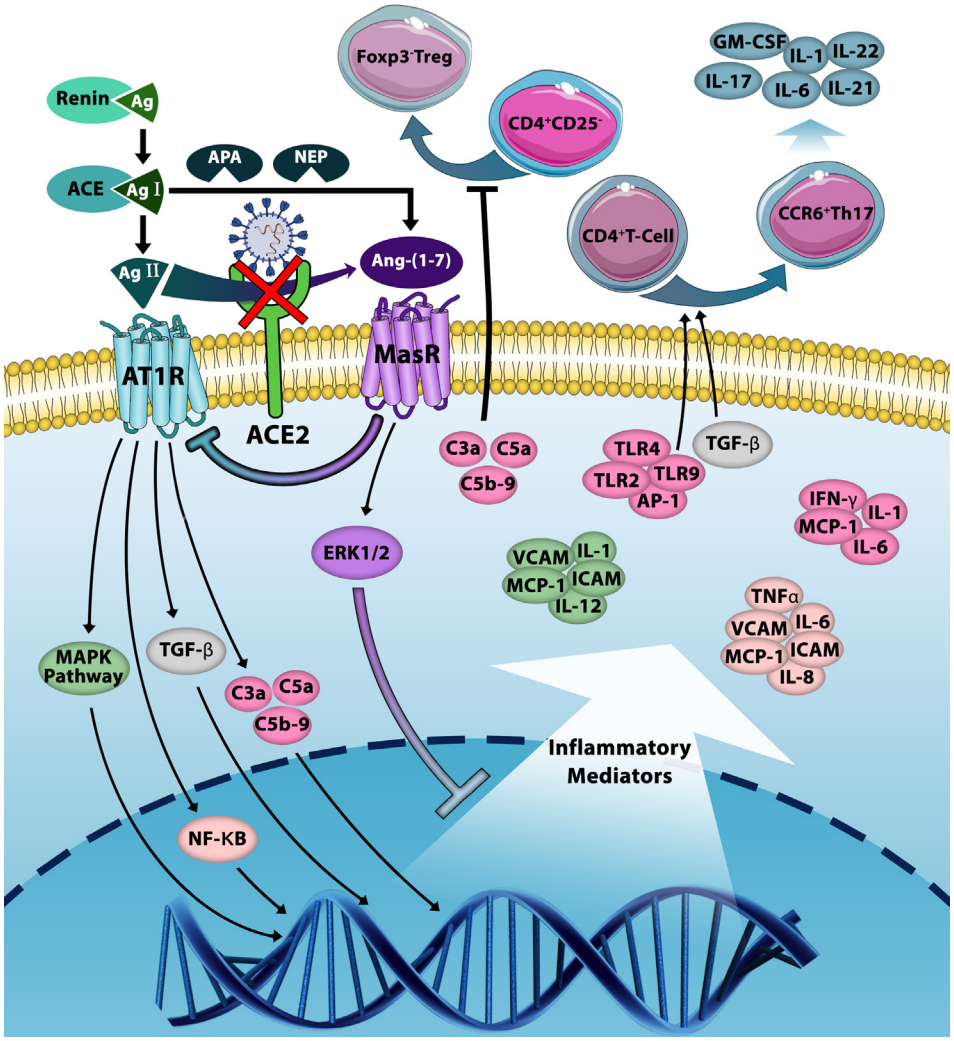

Fig. 2. ACE/Angiotensin II/AT1R and ACE2/MasR axis. The SARS-CoV-2 induced imbalance of ACE2/ACE that results in AT1R-mediated inflammatory response which will be accompanied with activation of the complement system, MAPK and NF-kB. The decrement of Ang (1–7) following SARS-CoV-2-mediated ACE2 down-regulation results in attenuation of MasR function. The MasR modulates AT1R-mediated inflammatory cytokine responses. Ang-(1–7) modulates the activity of ERK 1/2 via MasR. ERK 1/2 pathway induces production of IL-10, as an anti-inflammatory cytokine. Ang II, TLR2, TLR4, TLR9, and AP-1 transcription factor induce TGF-β expression. TGF-β has a role in the differentiation of T helper 17 cells from naive CD4+ T-cells.

ARDS [35].

Given the above premises, it seems reasonable to speculate that depletion of ACE2 and activation of ACE/Angiotensin II/AT1R axis might have a pivotal role in the clinical presentations of COVID-19. In fact, higher circulatory levels of Ang II were reported in COVID-19 patients than the control subjects and these plasma levels of Ang II were linearly associated with lung injury [36]. Therefore, in contrast to earlier clinical experts' opinions, RAAS inhibitors should not be discontinued in stable cases of COVID-19 because the discontinuation of ACE inhibitors and ARBs may potentially have detrimental effects on these patients [14,37,38]. In a recent study, the first clinical evidence has shown that ACE inhibitors or ARB therapy in COVID-19 patients with hypertension were associated with a lower rate of disease severity, a trend toward lower IL-6 levels, and higher circulatory CD3+ and CD4+ T cells counts [39].

The protective effect of ACE2 in severe acute lung failure has been shown in animal models [40]. The accumulating clinical-epidemiological evidence about COVID-19 implies that SARS-CoV-2 associated ACE2 depletion is accompanied with a severe clinical course of disease in those clinical and epidemiological conditions that jeopardize the levels of ACE2 expression including older age, male sex, and medical conditions (diabetes mellitus, hypertension and cardiovascular diseases, and obesity) [41,42]. Under these medical conditions, the COVID-19 infection-induced ACE2 depletion could not overcome already exaggerated ACE/Angiotensin II/AT1R axis activity. Hence, administration of recombinant soluble ACE2 to patients with severe COVID-19 infection may be a therapeutic modality. However, it is worthwhile to consider targeting downstream of ACE/Angiotensin II/AT1R axis, such as IL-6-STAT3 axis [34] to combat the observed cytokine storm in COVID-19 in order to prevent lung inflammation and end organ damage.

3. ACE2/MasR axis

ACE2, Ang-(1–7) and Ang-(1–7) receptor Mas are the constituents of the other arm of the RAS system which counteracts and attenuates the effects of ACE-Ang II-AT1R axis [43,44]. ACE2 derives vasodilatory peptide Ang-(1–7) from Ang II following a cleavage activity. This vasodilatory peptide has anti-proliferative, anti-thrombotic and anti-inflammatory activities [45–47].

Ang-(1–7) reduces the expression of p38 MAPK and NF-κB and inflammatory factors such as IL-6, TNFα and IL-8 [48–51]. Thus, Ang-(1–7) per se has an anti-inflammatory effect and ameliorates inflammatory damages, as revealed in several animal studies [52,53]. It has been shown that Ang-(1–7) reduces inflammatory cardiac injury in diabetic hypertensive rats [52] and glomerular involvement in mesangial proliferative glomerulonephritis (MPGN) rat models [53].

The protection of vascular endothelium and renal tubular cells, diuresis and vasodilation-dependent Ang-(1–7) effects occur via MasR [54,55]. Mas receptors express in the epithelium and bronchial smooth muscle; therefore, Ang (1–7) could modulate acute and chronic inflammatory processes in the lung via activation of MasR [56]. A range

of physiological effects of Ang- (1–7) is present in different tissues such as heart, brain and kidney by its action on MasR [57].

Ang-(1–7) also attenuates Ang II induced intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and MCP1 expression by MasR activation leading to inhibition of the p38MAPK and NF-κB pathways [58].

ERK 1/2 pathway modulates production of IL-10 [59] that induces differentiation of T-helper toward Th2-type. Th-2 regulates immune responses by producing anti-inflammatory cytokines like IL-4, IL-5, IL-9 and IL-13 [60]. Additionally, IL-10 is an anti-inflammatory cytokine that may be involved in the prevention of tissue damage [61,62]. Ang-(1–7) modulates the activity of ERK 1/2 (Fig. 2) [63–65].

Therefore, Ang-(1–7) has an anti-inflammatory function via modulation of NF-κB, MAPK and ERK 1/2 pathways. Hence, it may be proposed that SARS-CoV-2 associated suppression of ACE2, which would be accompanied with reduction of all Mas receptor-mediated functions, leads to accentuation of the cytokines release and frank inflammatory responses. Because Ang-(1–7) exerts a critical role in counteracting the pro-inflammatory effect of RAAS, protecting from endothelial cell activation and resulting lung damage from inflammatory mediators in the cytokine storm, the administration of Ang-(1–7) or one of its similar agents to patients with COVID-19 pneumonitis has been suggested [35,66].

4. ACE2 /DABK/ bradykinin B1 receptor axis

The kinin-kallikrein system includes kininogen, kallikrein enzyme, bradykinin (BK-1–9 or BK), and [des-Arg9]-BK or DABK [67,68]. The active products of this system interact with two distinct G-protein coupled receptors, the bradykinin B1 receptor (BKB1R) and bradykinin B2 receptor (BKB2R); the main ligand of BKB1R is DABK and the ligand of BKB2R is BK [69,70]. BKB1R could hardly be detected in peripheral tissues in normal states; however, it is expressed on the cell types involved in inflammation. Therefore, it is an inducible pro-inflammatory receptor [71]. The expression of BKB1R, as a specific receptor of bradykinin pathway, is highly sensitive to inflammatory mediators such as lipopolysaccharide (LPS) and interleukins [70,72–74]. It is also up-regulated by cytokines such as IL-1B and TNFα [75–77]. IL-2, IFNγ, epidermal growth factor (EGF), and oncostatin increase the rate of BKB1R receptor mediated response [77–80]. It should be mentioned that IL-1B and TNFα-induced BKB1R expression is related to NF-κB activity [81]. Sodhi et al.[82] showed that activation of BKB1R enhances the neutrophil attraction to tissue by release of chemokine C-X-C motif chemokine 5 (CXCL5). Activity of this receptor leads to expression of FGF-2 [83], and to increased levels of IL-1B [84] and MCP1 (Fig. 3) [85].

DABK is a known pulmonary inflammatory factor [86–89]. It is interesting that ACE2 also cleaves terminal residue of DABK [90,91]. This reaction results in deactivation of DABK. Therefore, it could be postulated that COVID-19-induced reduction of ACE2 activity would be accompanied with increased activity of DABK and the resulting accentuation of the aforementioned inflammatory cascade, leading to increased cytokine release. Hence, targeting the ACE2 /DABK/ Bradykinin B1 Receptor axis has been suggested by some authors [92,93]. to prevent or control ARDS in patients with severe COVID-19. Although several BKB1 antagonists have passed phase II clinical trials, none have been approved yet for clinical use [71].

5. C3a-C3aR/C5a-C5aR axis

The complement system is an ancient system that contributes to innate immune response. This system includes many proteins and cleavage products that plays a key functional role in defense against microorganisms including viruses. The viral inactivation by the complement cascade involves virus uptake and clearance by phagocytic cells, coating virions resulting in prevention of attachment with their receptors, virus lysis by pore formation, and destruction of its membrane by membrane attack complex formation (C5b-9) [94].

Following viral-induced complement cascade activation, inflammatory processes are promoted. Complement factor 5a (C5a) is the strongest inflammatory peptide in the complement cascade that induces release of pro-inflammatory cytokines [95–98].]. C5a can also induce secretion of TNF-α [99,100]. Terminal products of the complement cascade can induce the production of cytokines such as TNF-α and IL-1 [98,101–104]. Terminal complement component C5b-9 induces release of IL-6 via activation of redox-sensitive transcription factor NF-κB and Activator Protein-1 (AP-1) [105] and Monocyte Chemoattractant protein-1 (MCP1) from vascular smooth muscle cells [106]. Also, the increased production of C3a leads to production of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α [107].

The involvement of the complement system in the pathogenesis of syncytial virus infection, MERS-CoV and SARS-CoV has been examined in several studies [108–110]. The hyperactivation of complement components including C5a in sera and C5b-9 in lungs was observed in MERS-CoV-infected hDPP4-transgenic mice. The lung and spleen-induced pathological damages and inflammatory responses were alleviated through blockade of the C5a–C5aR axis in those transgenic mice [110].

Gralinski et al. [109] showed that mice models deficient in C3(C3-/-) loads in the lung had milder SARS-CoV induced pathologic features such as better respiratory function, lower weight loss, reduced pathologic findings in respiratory system, and lower circulatory and tissue cytokines and chemokines, despite equal lung viral loads compared to the controls. These results showed that although the complement system had no role in virus replication, activation of complement system in the lungs of SARS-CoV infected mice might lead to immune mediated damages in the lungs [109].

The complement cascade can be activated by the lectin pathway (Fig. 4). By priming the immune system and enhancing clearances of viruses and virus-infected cells [111]], the lectin pathway may also be involved in COVID-19 pathogenesis. Recently, Gao et al. [108] reported in a very interesting study the involvement of complement cascade aberrant activation in the pathogenesis of SARS/MERS-CoV or SARS-CoV-2 via viral nucleocapsid (N) protein-mediated MASP-2 auto-activation and binding to mannose-binding lectin (MLB). MASP-2 is the main serine protease in the lectin pathway that induces downstream complement cascade via the MLB pathway resulting in accelerated inflammatory responses and lung damages. In another arm of the aforementioned study, the contribution of SARS-CoV-2 N protein in activation of the complement cascade was investigated in lungs of patients who expired with COVID-19. Not only were deposition of the complement components including C3, C3a and C5b-9 observed in lung autopsies, but elevated circulatory levels of C5a were also reported in severe cases of COVID-19 [108].

Magro et al. [112] reported a pauci-inflammatory changes and lack of viral cytopathic effects accompanied with heavy deposition of C5b-9, C4d and MBL-MASP2 in lung septal vasculatures of 5 patients with COVID-19-induced respiratory failure, indicative of unrestrained activation of the alternative and lectin cascades in these patients.

Given the above animal and clinical studies, it is tempting to target the components of complement in severe COVID-19. A promising clinical response including increased lung oxygenation and alleviation of systemic inflammation was reported in two patients with COVID-19 who received an anti-C5a antibody [108].

C5a, as the most potent complement derived mediator of inflammation in response to infections, increases production of IL-6, TNFα and IL-1 from Toll-Like Receptor (TLR-2, TLR-4, TLR-9) stimulated macrophages [113,114]. However, the C5a-C5R axis inhibition by the available pharmaceutical agents would be partial, and the activity of residual terminal complement components might remain. Therefore, targeting the upstream activators of the complement cascade such as C3a-C3aR axis may be more effective in restraining the uncontrolled

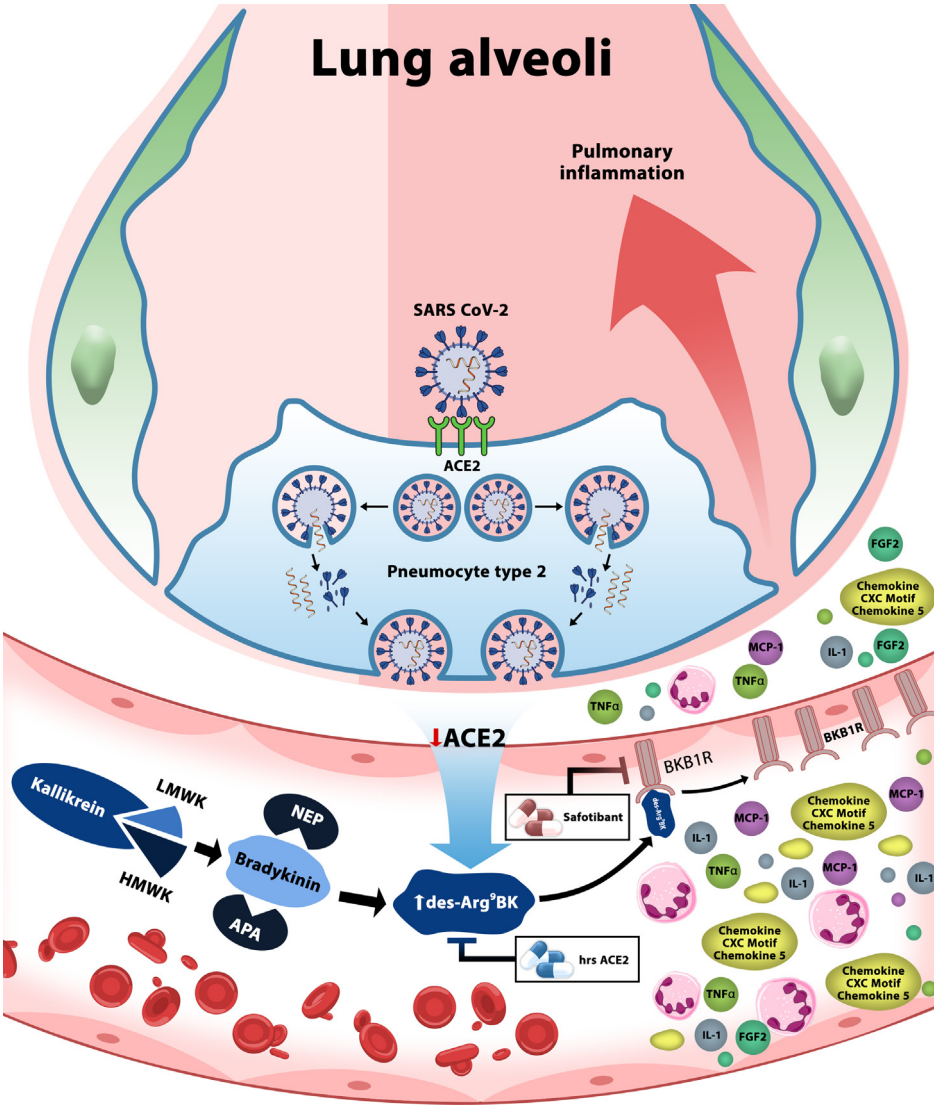

Fig. 3. ACE2/Bradykinin B1R/DABK axis. Down-regulation of ACE2 by SARS-CoV-2 leads to increased activity of [des-Arg9]-BK (DABK) with resulting increased inflammatory cytokine responses. Safotibant is a promising drug to antagonize BKB1R.

complement pathway activation in severe COVID-19 [115]. Very recently, the compstatin-based complement C3 inhibitor AMY-101 was administered to a patient with ARDS due to COVID-19, in which very good clinical responses with a high level of safety were reported [116].

The overall clinical benefits of targeting the C3a-C3aR/C5a-C5aR axis in order to control maladaptive immune-inflammatory consequences of the complement pathways in severe COVID-19 remains to be clarified in the near future.

6. Covid-19 cytokine storm is a complex network

The Covid-19 cytokine storm, like the other cytokine storms in infectious and non-infectious conditions, may be considered as a complex network. The complex network of the cytokine response was described by Tisoncik et al. [7] as “a series of overlapping networks, each with a degree of redundancy and with alternative pathways”.

Our aforementioned pathogenesis of the so-called COVID-19 cytokine storm through the four described distinct axes clarified that this cytokine storm complex network has many components which might cross-talk with each other in multiple known and unknown interfaces. These interactions in a network state imply the complex nature of the COVID-19 cytokine storm. The dynamic equilibrium of the network components could be disturbed at multiple sites to emerge an untoward behavior. In COVID-19 cytokine storm, this perturbation is initiated via attachment of the SARS-CoV-2 spike protein to its receptor, ACE2, followed by the ACE/Ang II/AT1R axis activation leading to hyperactivation of NF-κB by IL-6 STATs axis [34]. In the normal dynamic equilibrium state, the ACE/Ang II/AT1R axis activation is counterbalanced by ACE2/MasR axis and production of Ang-(1–7) that reduces the expression of p38 MAPK and NF-κB and inflammatory factors such as IL-6, TNFα and IL-8 [49–51]. However, SARS-CoV-2 associated down-regulation of ACE2 suppresses these immunomodulatory effects, leading to accentuation of the cytokine release response.

We currently know that DABK is a pulmonary inflammatory factor whose deactivation by ACE2 is deranged by COVID-19-induced reduction of ACE2 activity. This derangement is followed by ACE2 /DABK/ Bradykinin B1 Receptor axis activation that creates a pro-inflammatory synergistic effect for SARS-CoV-2 associated ACE/Ang II/AT1R axis activation. The resulting effect would be a more inflammatory state, neutrophil recruitment and enhancement of pathological pulmonary changes that are observed in ARDS of severe COVID-19.

We have already discussed the involvement of the complement system in the pathogenesis of SARS-CoV-2 via its nucleocapsid (N) protein-mediated MASP-2 auto-activation and binding to MLB in the

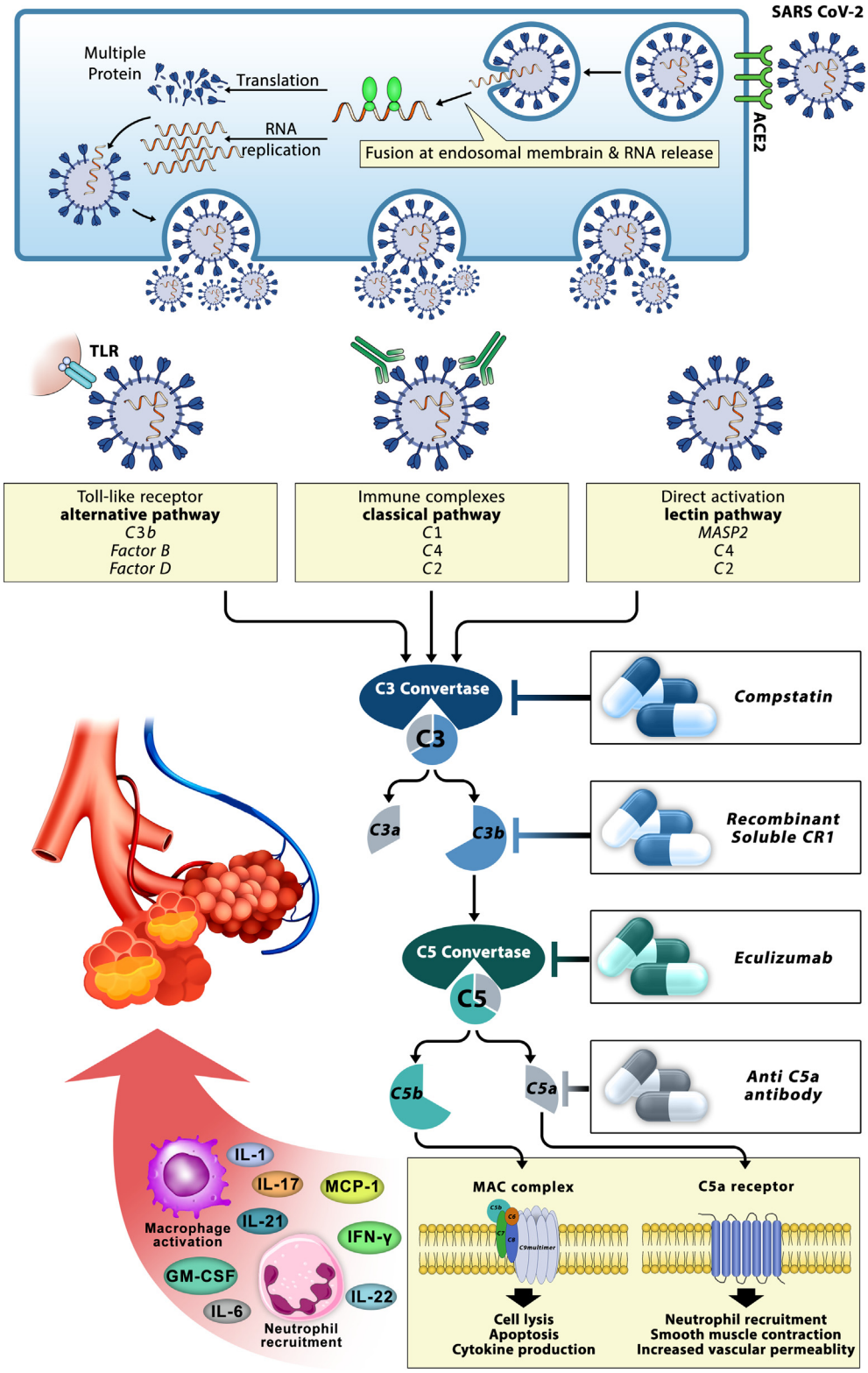

Fig. 4. The complement system activation and its inhibitors. The complement system is activated through classical, lectin and alternative pathways. The nucleocapsid protein of SARS-CoV-2 results in aberrant production of C3 through MASP-2 mediated activation of mannose-binding lectin (MBL).

lectin arm of C3a-C3aR/C5a-C5aR axis [108]. However, the increased production of Ang II and activation of AT1R may be accompanied with pro-inflammatory response via activation of the complement cascade including C5a, C5b-9 [23]. This implies a cross-talk between ACE/Angiotensin II/AT1R axis and the complement system.

Similar to other complex networks, elements from the complex network of the COVID-19 cytokine storm may experience much cross-talk with elements from known and unknown pathways and networks. For example, Ang II as an element from ACE/Ang II/AT1R induces TGF-β expression [22,117]. TGF-β has a role in the differentiation of T helper 17 cells from naive CD4+ T-cells. Th-17 cells generate IL-17, GM-CSF, IL-21 and IL-22. IL-17 itself promotes the production of a vast

Table 1
Therapeutic options for cytokine storm of COVID-19 based on underlying possible mechanisms.

Possible axis	Therapeutic option	Reference
ACE2	Recombinant hACE2	Basu et al. [121] Zhang et al. [122] Imai et al. [40] Gu et al. [124]
Complement system	Anti C5 (eculizumab)	Thurman et al. [129]
	Anti C3 (compstatin)	Zhang et al. [114]
	Recombinant CR1	Williams et al. [120]
	Therapeutic plasma exchange	
BRB1R/DABK	BKB1R antagonist (safotibant)	Porreca et al. [126] Barth et al. [127] Qadri et al. [71]

ACE2: Angiotensin-converting enzyme-2; CR1: complement receptor1; BKB1R: bradykinin B 1 receptor; DABK: des-Arg9-bradykinin.

amount of pro-inflammatory cytokines and chemokines [8,118]. IL-17 was among the cytokines that were significantly correlated with the lung injury Murray score and disease severity in COVID-19 [119]. An increment of the highly pro-inflammatory CCR6+ Th17 in CD4 T cells was reported in COVID-19 associated with ARDS [9]. Therefore, targeting IL-17 and T helper 17 responses in the cytokine storm of COVID-19 have been suggested [8,118].

From a unifying point of view, systems medicine approaches are required to understand the interactions among the different elements of the complex network of the COVID-19 cytokine storm. Undoubtedly, the clarification of hierarchy of the components of this complex network across different organizational levels will expand our armamentarium of treatments to tackle COVID-19.

7. Targeting cytokine storm

Therapeutic plasma exchange is a well-known therapeutic option that can be considered in the treatment of autoimmune diseases. The beneficial effect of this modality works through elimination of autoantibodies, complement components, immune complexes and cytokines. Therefore, this option may be valuable in the treatment of severe COVID-19 [120]. However, application of this therapeutic modality is a general approach to confront the cytokine storm. Hence, other approaches may be considered in the treatment of the COVID-19 driven cytokine storm in order to protect lungs from injury (Table 1).

According to the aforementioned axes which may be involved in the cytokine storm of severe cases of COVID-19, some potential targets could be considered as therapeutic options.

The first one is recombinant human ACE2. There are some trials regarding the efficacy and safety of this agent in clinicopathological settings related to ACE2 decrement such as congestive heart failure (CHF) [121], ARDS [122,123], and lung injury due to viral illness such as respiratory syncytial virus (RSV) [124]. The reported findings about safety and efficacy were promising. Very recently, Monteil et al.[125] reported that human recombinant soluble ACE2 (hrsACE2) can prevent entry of SARS-C0V-2 to the human blood vessel organoid and human kidney organoid; this finding may suggest a highly compelling therapeutic intervention to protect lung injury in COVID-19.

We suggested ACE2/Bradykinin/DABK may be involved in the inflammatory response of SARS CoV-2; therefore, blockade of this axis by inhibiting BKB1R may ameliorate a part of the cytokine storm which occurs in COVID-19 infection. LF22-0542 (Safotibant) is a BKB1R antagonist with promising anti-inflammatory results [126,127]. Several clinical trials have been conducted to evaluate the effect of this drug in multiple medical settings; they have had promising results (Fig. 3) [71].

Regarding the pivotal role of the complement system in the cytokine storm and activation of Th-17, every effort should be made to suppress the activation of this elegant cascade. C5a, as a potent component of this system, is a good target for alleviation of pro-inflammatory responses to severe COVID-19. Eculizumab is a monoclonal antibody with high affinity to C5 near its cleavage site [128]. This agent prevents the formation of C5a and C5b-9. It has been reported that this monoclonal antibody has beneficial effects in the treatment of diseases where their pathogenesis are based on complement activation [129]. In a preliminary study conducted by Gao et al. [108], two patients with severe COVID-19 received anti-C5a antibodies. Although the final effect of this type of therapeutic modality remains to be published, the two patients showed dramatic clinical responses [108].

C3 blockade is another component of the complement system that can be targeted. Compstatin is a cyclic inhibitor of C3 cleavage [129] that may be considered in severe COVID-19. Complement Receptor1 (CR1) is a cofactor to inactivate C3b and C4b and inhibits the activation of C3 through all active pathways. The recombinant form of soluble CR1 is developed, which can block complement activation in serum samples from patients with C3-glomerulonephritis (Fig. 4) [130].

In conclusion, accumulating evidence suggests that SARS-CoV-2 driven ACE2 down-regulation leads to an array of complex and intertwined molecular interactions via at least four axes consisting of dysregulation of the ACE/angiotensin II/AT1R axis, attenuation of ACE2/MasR axis, increased activation of ACE2/bradykinin B1R/DABK axis, and activation of the complement cascades, resulting in the observed cytokine storm in severe COVID-19.

The elucidation of molecular events of the aforementioned axes which might be involved in the pathogenesis of ARDS and lung injury in fulminant infections with SARS-Co-V-2 will promise novel therapeutic options for prevention or attenuation of the inflammatory cytokine release response that are observed nowadays in patients with severe COVID-19.

8. Authors' contributions

MM, IN, JR, SF and MK interpreted and wrote the manuscript. IN and MM supervised the study. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: An award was given to Iraj Nabipour by “Novo Nordisk Pars” (The Best Innovator of Diabetes in Iran 2013). For the remaining authors none were declared.

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