Review

COVID-19 and kidney injury: Could Renin-Angiotensin components crosstalk with immune responses?

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Abstract: Coronavirus disease 2019 (COVID-19) is a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To contain the virus, numerous preventive measures have been taken including isolation of patients, careful infection control, social distancing, and taking vaccine. So far, new confirmed and death cases are still increasing. SARS-CoV-2 invades cells by using the angiotensin converting enzyme 2 (ACE2). ACE2 is an essential enzyme of the renin-angiotensin system (RAS) which converts angiotensin II (Ang II) to angiotensin (1-7). ACE2 is expressed in different organs, including lung, heart, and kidney. A high number of COVID-19 patients developed kidney injury has been reported. Renal impairment and acute injury are associated with mortality of COVID-19, which is 14-16 times higher than other general patients. Acute Kidney Injury has been occured in 2.9 up to 43% of intensive care unit patients. The increasing evidence show that the components of RAS can activate the complement cascade, and cytokines production. Kidney injury caused by SARS-CoV-2 is related mainly to systemic and local inflammation. Moreover, the uncontrolled immune responses mediated by SARS-CoV-2 including hypercytokinaemia, secondary hemophagocytic lymphohistiocytosis, antibody dependent enhancement, complement system, and phagocytic cells activation can contribute in the virus pathogenesis leading to associated renal dysfunction. However, the role and crosstalk between of RAS components and immune response in mediating kidney injury remain undefined. In this review, we focus on the recent studies to provide the pathogenesis of SARS-CoV-2 interacting with RAS and immune responses to mediate kidney injury.

Keywords: SARS-CoV-2; RAS; acute kidney injury; immune response

1. Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic and its impact on human has been immense. To contain the virus, numerous preventive measures have been taken such as isolation of patients, careful infection control, social distancing, and taking vaccine. So far, new confirmed and death cases are still increasing.

SARS-CoV-2 gets access to the human body, mainly via the upper respiratory tract and invades the target organs like the lower respiratory tract**.** Moreover, it may circulate in the peripheral blood stream to invade other organs via ACE2 receptors [1]. After infecting the lungs, it stimulates the local immune responses such as the recruitment of inflammatory cells, including macrophages and monocytes. It has been reported that phagocytic cells correlate with the lung damage in critically COVID-19 patients, and also the acute respiratory illness with diffuse alveolar hemorrhage and acute respiratory failure are the early character of COVID-19 [2]. The immune responses usually have the capability of clearing the infected cells, and producing the antibodies which inactivate the virus.

However, a dysregulation of immune responses can lead to the local and systemic pathology due to systemic cytokine storms. Hence, SARS-CoV-2 causes the other organs injury by activating the overproduction immune responses, which may eventually increase the morbidity and mortality of COVID-19. In this review, we focus on kidney injury caused by SARS-CoV-2.

2. Pathogenesis of SARS-CoV-2 in kidney

Kidney injury caused by SARS-CoV-2 may be related to the systemic and local inflammation. Different studies of immunological data for patients with COVID-19 revealing that the increased cytokines can mediate the hyper-inflammatory responses which can contribute a lot in amplifying acute kidney injury (AKI) as summarized in Table 1. The kidney histology from autopsies of COVID-19 shows the severe acute tubular necrosis with lymphocyte and macrophage infiltration, clotting and disseminated intravascular coagulation with small vessel thrombosis [3]. Uncontrolled pro-coagulation factors and complement system are known to activate each other which can intensify the pathogenesis of SARS-CoV-2 in kidney by inducing the inflammatory mediators [4]. Renal impairment and acute injury have been documented to be associated with mortality of COVID-19, which is 14-16 times higher than other general patients [5]. It is known that renal impairment is associated with hematuria, proteinuria, and higher creatinine due to kidney cell injury and these features have been reported in COVID-19 patients. A consecutive study of 701 COVID-19 patients in Wuhan, China reported that 43.9% of patients had proteinuria, 26.7% had hematuria [6]. AKI has been reported as a significant complication of the COVIV-19 to occur in 2.9 up to 43% of intensive care unit patients [7]. Another study of 5,449 COVID-19 patients found that AKI patients developed at the rate of 36.6% were 35% died and 14.3-20% required renal replacement therapy (RRT) [8]. Moreover, a recent observational study carried out in a tertiary care hospital in Milan, Italy shows that among 99 patients, 75% developed AKI [9].

AKI process was suspected to be associated with the systemic circulation of SARS-CoV-2 as it was detected in urine samples of patients with COVID-19 [10]. Also, the residues of SARS-CoV-2 nucleocapsid protein were found in the kidney tubules and its clusters particles were found in tubular epithelium and podocytes [11]. However, Kudose et al., did not get a great evidence of a direct SARS-CoV-2 invasion in AKI [12]. Another recent study has been carried out on COVID-19 patients with AKI shows the acute tubular necrosis, but found no evidence of virus particles in kidney biopsy [13]. Totally, although the kidneys are not highly exposed to SARS-CoV-2 invasion compared to the lungs, the virus might mediate AKI in multiple mechanisms such as a direct invasion, and the intervention of cytokine production.

Table 1. Features of immune responses in COVID-19 patients.

Methodology of the study.	Results	Conclusion	Reference
A retrospective study analyzed clinical and laboratory data of 88 hospitalization patients with COVID-19	In critically patients, 86% have Lymphopenia, above 70% have increased IL-2R, IL-6 and TNF-α	Inflammatory cytokines may correlate with severity of a disease	(Xu et al., 2020) [60]
Clinical and immunologic data were analyzed in 71 patients with COVID-19	Natural killer cells, complement C1q, T and B lymphocytes, cells were reduced while IL-6, neutrophils, CRP were increased	Dysregulation of immune response and pro-inflammatory cytokines may contribute to the cytokine storms	(Wu et al., 2020) [53]
Clinical and immunologic markers were analyzed in retrospective study of 21 patients with COVID-19	Absolute number of CD4 and CD8 T cells were reduced while IL-2R, IL-6, and TNF-α were increased	A reduction of T lymphocytes may result in severity of a disease	(Chen et al., 2020) [54]
A study analyzed the plasma cytokines of 53 patients with COVID-19	IL-1, IL-7, IL-10, GSFC, IP-10, MCP-3, IFN-γ, IL-2, IL-18, and MIP1A were increased in patients compared to the healthy control	SARS-CoV-2 can stimulate the cytokines release which intensify the severity of a disease	(Yang et al., 2020) [55]

3. Mechanisms of acute kidney injury caused by SARS-CoV-2

The AKI caused by SARS-CoV-2 is mediated by several factors, we review the possible multi-factorials underlying mechanisms of acute kidney injury include a direct viral toxicity, immune pathology (Fig. 1)

4. Cytopathic effects

The evidence shows that nsp10 of SARS-CoV interacts with cytochrome oxidase and NADH 4L to disturb the normal functioning of mitochondria thereby causing cell injury [14]. In addition, a recent report shows that SARS-CoV-2 in type II alveolar pneumocytes induces focal lung injury, a cytopathic effect [15]. Similar evidence shows that SARS-CoV-2 invades directly human kidney cells include proximal tubular epithelial cells (PTEC) where viral replication may result in a cytopathic effect [16]. Thus, SARS-CoV-2 can infect PTEC, glomerular mesangial cells, and glomerular epithelial cells (podocytes) which exhibit its AC2 receptor to induce AKI by direct cytopathogenic effects. However, an extent of a direct infection to mediate kidney pathology remains unknown.

5. Immune response and SARS-CoV-2: PAMP in the pathogenesis of SARS-COV-2

Immune cells like phagocytic cells are activated through their ability of recognizing the pathogen-associated molecular patterns (PAMP) including unmethylated double-stranded DNA (CpG), single stranded RNA, flagellin, lipoproteins and lipopolysaccharides of pathogens using PRR on the cell membrane [17]. PAMP and their carboxyl-terminal domain interact with Toll/interleukin-1 Receptor (TIR) -containing adaptors leading to activation of a downstream signal transduction [18]. Recognition of viral PAMPs by TLRs on macrophages activates the innate immune response by recruiting signal transfer proteins such as MyD88, TRAM, TRIF in the cytoplasmic TIR domain followed by phosphorylation of different kinases including IRAKs, TBK1, and IKKs and tumor necrosis factor receptor-related factor-6 (TRAF-6) according to the different adaptors, eventually lead to activation of the NF-κB, MAPK, PI3K, JNK, STAT, interferon (IFN) pathways that promote the transcription of inflammatory cytokines including IFN, IL-1β, IL-6, and others which coordinate the local and systemic inflammatory responses [19]. It has been reported that TLRs play a great role in recognizing SARS-CoV infection where TRAM -/-, TLR3-/- and TRL4-/- mice were at risk to be affected by SARS-CoV than wild mouse counterpart [20]. SARS-CoV S protein has been documented to stimulate the immune

responses through the activation of NF-κB pathway. The interaction between SARS-CoV-2 proteins with TLRs is a worth studying in the future.

6. SARS-CoV-2 and Cytokines

The effect of IFN production involves in activating the immune cells like CD8+ cytotoxic T which detects the viral peptides displayed on class I major histocompatibility complex (MHC-I) proteins and lyses the infected cells, followed with the elevation of CD4+T cells which detects the viral peptides on MHC-II of macrophages. B lymphocytes can be stimulated and crosstalk with CD4+T cells, leading in the production of IgM and IgG antibodies [21]. The current study shows that the severity of COVID-19 is associated with lymphopenia [22]. Morbidity and mortality of SARS-CoV- 2 patients can be associated with a decreased level of white blood cells and lymphocytes count in COVID-19. The pathway mediated by SARS-CoV-2 to induce the apoptosis of T cells remains unclear. Interestingly, another study demonstrated that even the number of CD4+ and CD8+T cells in the peripheral blood are reduced, but that these cells are highly activated and also correlate with increased levels of CD4+ T cytokines, INF-γ, TNF-α, IL-2, and IL-17 in COVID-19 patients compared to the control group [23]. COVID-19 patients admitted in ICU compared to non-ICU had higher concentration of cytokines, including MIP1A, TNF-α, IL-2, IP-10, GSCF, and MCP-1 [24]. The production of cytokines is beneficial as they can recruit the inflammatory cells, however, upregulation and overproduction of cytokines such as IL-1β, TNF, and IL-6 mediates an acute generalized inflammatory response resulting in septic shock [24]. Several studies have determined the role of different cytokines in AKI where IFN-γ, IL-6, and MCP-1 have been associated with AKI due to Th1 and Th2 activation in animal models of ischemic-reperfusion injury (IRI) [26] and Tumor necrosis factor like weak inducer of apoptosis (TWEAK) has been participating in renal tubular cell injury [27]. IL-6 receptor blocker (Tocilizumab) and IL-1 antagonist have been proposed to weaken the hyper-inflammation induced by SARS-CoV-2 [28].However, the virus adapts several ways of escaping the immune response as type I and III interferon responses has been documented to be suppressed in SARS [29] and anti-Spike antibodies urged the excessive inflammatory factor production, including IL-8, IL-6, IL-1β, and TNF by human M2 macrophages, which subsequently disrupt the endothelial barrier membrane integrity and mediates microvascular thrombosis in severe cases of COVID-19 [30]. More increasing evidences show that SARS-CoV-2 can evade immune responses and induce hyper-inflammatory responses. The systematic inflammation can induce the Kidney impairment. However, the mechanism of immune evasion used by SARS-CoV-2 remains unclear.

7. SARS-CoV-2 and sHLH

The secondary hemophagocytic lymphohistiocytosis (sHLH) refers to the immune cells that become overactive and T helper cells trigger too much inflammatory cytokines while macrophages destroy the host immune cells by engulfing the leukocytes and their precursor cells [31]. sHLH has been a rare disease which associated with genetic, neoplastic, autoimmune, and infectious diseases. However, the different features of sHLH including high fever, abnormal hepatic enzyme levels, cytopenia, and high level of cytokine such as interleukin IL-2, IL-7, GCSF, IP10, MIP1A and TNF-α have been associated with COVID-19 severity [32]. The mechanism of immune and inflammatory response caused by sHLH is still unknown, Thus, further studies are needed to elucidate details of sHLH about immune and inflammatory response to SARS-CoV-2 infection and Kidney injury.

8. SARS-CoV-2 and Antibody dependent enhancement

Antibody production plays a vital role in clearing the intruders in the cells, but, the antibody dependent enhancement (ADE) improves its entry into host cells and

ameliorates its infectivity and virulence. ADE has been reported in SARS-CoV, and feline infectious peritonitis virus (FIPV) where monoclonal antibody Ab binds to the cell surface IgG Fc receptor, which later facilitates the virus to enter inside immune cells [33]. A recent report documents that the Ebola virus stimulates the antibody to bind to its glycoprotein and followed with the complement C1 which binds to the Fc part of the antibody leading to the enhancement of the virus using endocytosis or receptors of the target cells [34]. Similar study shows that the antigens of MERS bind to an antibody which allows the virus to use its IgG Fc receptors to enter these immune cells [35]. ADE may eventually distribute this virus to other parts the host cells end up with AKI and multi-organs failure. Therefore, ADE can mediate immune responses and induces inflammatory responses, lymphopenia and cytokine storm. However, the role of ADE in SARS-CoV-2 pathogenesis and the molecular mechanism is not well-known. This should be clarified in the future in order to assess the safety of SARS-COV-2 vaccine and inaugurate proper strategies for new emerges infection in the future.

### 9. SARS-CoV-2 and Complement system

The complement system eliminates the viruses by different mechanisms, including a direct neutralization of cell-free virus, destruction of virus-cell infected, and urges the specific immune response. The uncontrolled of complement activation can mediate autoimmune and severe inflammatory responses [36].

It has been reported that N proteins of SARS-CoV, MERS-CoV interacts with MASP-2, a regulatory protein in the lectin pathway of complement activation, resulting high inflammatory responses and abnormal complement C5 activation and then induces lung cell injury [37]. A recent study shows the role of complement activation in mediating acute respiratory failure-associated with SARS-CoV-2 [38]. No significant cytopathic effects were observed while the deposition of C5b-9, C4d and MASP-2 appeared [39]. In addition, it has been reported that the autopsy from COVI-19 patients shows a microangiopathy and microvascular coagulation which can be induced by complement activation. Moreover, the C5b-9 concentration is high in the AKI patient compared to the patient without AKI [40].

SARS-CoV-2 infection can activate complement system to induce kidney injury by classical, alternative, and lectin pathways. However, a renin which has enzymatic activity on the complement C3 can split it into C3a and C3b due to a positive feedback from unregulated RAS components (Fig. 2) [41]. Moreover, complement C5b-9 deposition forms a lytic pole in the outer membrane of kidney cells, then release proinflammatory cytokines, vasoactive chemicals, and reactive oxygen species which will contribute to the pathogenesis of AKI [42]. It has been also reported that C5a can induce pro-inflammatory chemokines produced with neutrophils dependent or independent pathways to mediate renal injury [43,44]. Several antibodies, peptide, RNA interference are being used to block the complement molecules. Interestingly, complement inhibitor like Eculizumab showed to be effective in the treatment of COVID-19 [45].

Taken together, the immune systems perform an incomparable role in fighting against an intruder like SARS-CoV-2. The involvement and intercommunication between innate and adaptive immunity recruit the immune cells and produce different cytokines in a regulated manner. The immune responses and inflammatory cytokines are coordinated by the complement cascade activation. However, hyper-stimulation of the immune responses and accompanied with camouflaged virus may result in host cell injury and correlate with AKI and multi-organs failure. Therefore, more clarification on the complement system and immune responses in general with their impact on the kidney will be highlighted in the future.
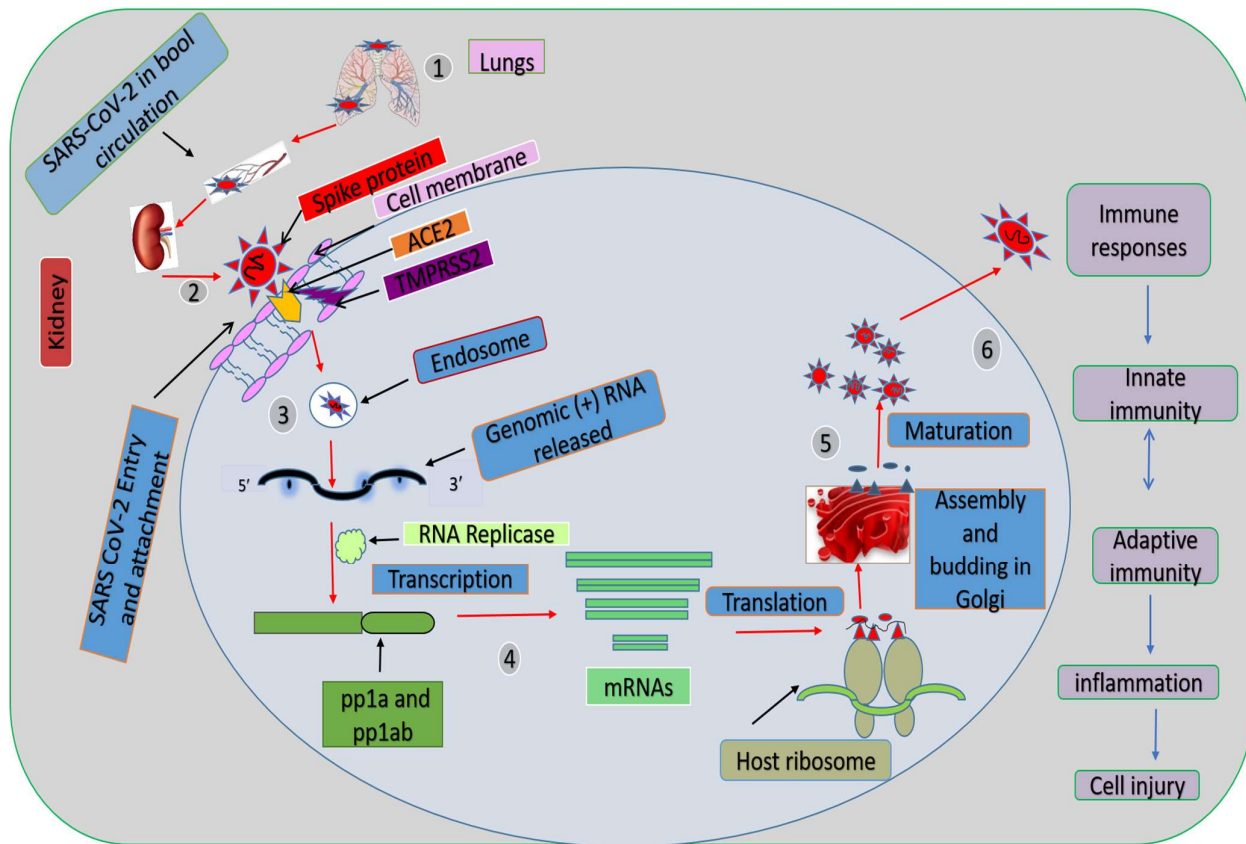
Figure 1. SARS-CoV-2 pathogenesis and AKI.

SARS-CoV-2 pathogenesis and AKI: SARS-CoV-2 invades host cells by using upper airways, reaching to the lungs. The virus can circulate in the blood reaching to different organs including kidney. Inside the host cells, SARS-CoV-2 undergoes its cycle replication resulting in the cell lysis. In this time, more immune response can be produced resulting in the systemic inflammation due to cytokine storm.

10. Immune response and SARS-CoV-2: Renin-angiotensin system and AKI

Renin - angiotensin system (RAS) is known to regulate the fundamental processes of cardiovascular homeostasis such as balancing blood pressure, body fluid, electrolyte, and maintaining the vascular tone. It starts with juxtaglomerular apparatus in macula densa of the kidney which detects the decline in renal blood flow and then converts prorenin by neuroendocrine convertase 1 into renin enzyme [46]. Renin converts angiotensinogen into angiotensin I, which is then converted to Ang II by angiotensin converting enzyme (ACE). ACE2 is a type I transmembrane glycoprotein belongs to the zinc-dependent metallopeptidases in the metzincins superfamily which cleaves an amino acids group of the Ang II to form angiotensin-(1-7) thence weakening its effects on vasoconstriction and sodium ($\downarrow$Na+) reabsorption [47]. On the other hand, Ang II stimulates the production of Anti-Diuretic Hormone (ADH) and aldosterone hormone thereby mediating the reabsorption of water and Na+ respectively, leading to the constriction of blood vessels and elevation of blood pressure and extracellular body fluid [48]. The main question is if RAS is involving in the SARS-CoV-2 pathogenesis. A recent report has shown the association between a reduced serum Na+ concentration and the severity COVID-19 [49]. A similar study shows the mean differences of Na+ concentrations in critical COVID-19 patients having 136.6 mmol/L whereas in mild patients having 139.2 mmol/L [50]. These reports reveal the pathophysiology of SARS-CoV-2 in interacting with RAS components and changing the

normal physiology of the kidney organ leading to the severity of the disease. We propose that SARS-CoV-2 can crosstalk with RAS components in mediating immune response resulting in kidney impairment. Therefore, it is paramount to review the role of RAS components in regulating the immune response, including the production of different cytokines.

RAS components have been shown to mediate the immune responses by promoting the inflammatory mediator production (Fig.2). For instance, Ang II mediates pro-inflammatory responses by controlling a transcription factor, nuclear factor-kappa B (NF-κB) and produces different cytokines including TNF-α, IL-1, IL-6, ICAM, VCAM-1, MCP-1, MMP-1, MMP-9, TGF-β, and AP-1. In addition, Ang II can also promote renal injury by changing the stability of helper T-cell (Th), producing the interferon-γ, and reducing the IL-4 level [51]. Moreover, angiotensin-(1-7) enhances vasodilatation by increasing nitric oxide bioavailability via Mas oncogene receptor. The nitric oxide plays a role in regulation and activation of the immune and inflammatory mediators, including T lymphocytes, macrophages, natural killer cells, mast cells and neutrophils [52]. The role of RAS components in mediating AKI has been documented where COVID-19 patients with AKI had the increased plasma RAS components compared to the patients without AKI as shown in Table 2.

SARS-CoV-2 enters the cells by using ACE2 where it may end up with a reduced ACE2 and promotes the raise of a pro-inflammatory mediators Ang II, and imbalance of RAS components, which will eventually trigger the immune responses, complement activation, and impairment of different organs including kidney. However, the molecular mechanism of RAS in mediating the immune response induced by SARS-CoV-2 remains uncertain. Therefore, more studies are highly needed to explore the interaction and regulation of systemic inflammation mediated by the crosstalk of RAS and SARS-CoV-2. More understanding of this mechanism can open a new look of how to tackle this health threat.

Table 2. Role of RAS components in mediating AKI.

Methodology of the study	Results	Conclusion	Reference
COVID-19 patients with AKI admitted to the ICU of St Louis Hospital were screened the levels of plasma Renin and aldosterone	Patients with AKI had an increased level of renin and aldosterone compare to patients without AKI	Activation of RAS is linked with AKI in COVID-19	(Dudoignon et al., 2020) [56]
Non diabetic and induced diabetic rat were subjected to AKI, and then treated with an AT2R agonist, C21, ACE2 activator	Plasma ACE, AT2R, Ang II were increased, while ACE2, Ang-(1-7) were reduced followed by renal injury	AT2R and ACE, and Ang II can mediate AKI	(Sharma et al., 2019) [57]
To determine the role of Ang II AT1R in Malaria-induced AKI, C57BL/6 mice were infected with *Plasmodium berghei* ANKA (PbA) and control mice treated with losartan (antagonist of AT1R) and captopril (antagonist of ACE)	The high levels of plasma creatinine and blood urea nitrogen were associated with a reduction in creatinine clearance, and glomerular hyper-cellularity, he high proteinuria and collagen deposition and interstitial space and was associated with pro-inflammatory cytokines were	Ang II/AT1R mediates an elevation of pro-inflammatory cytokines which in turn leads to AKI	(Silva et al., 2018) [58]

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	observed in PbA infected mice compared to the control mice	
To determine the role of Ang-(1-7) in kidney injury, Col4a3 −/− mice used as albert syndrome model and treated with Ang-(1-7) while wild mice type treated with saline	Ang-(1-7) treatment diminish the production of inflammatory cytokines and adhesion molecules and apoptosis reduced in kidney cells	Ang-(1-7) reduces kidney injury in Alport syndrome experimental (Choi et al., 2020) [59]
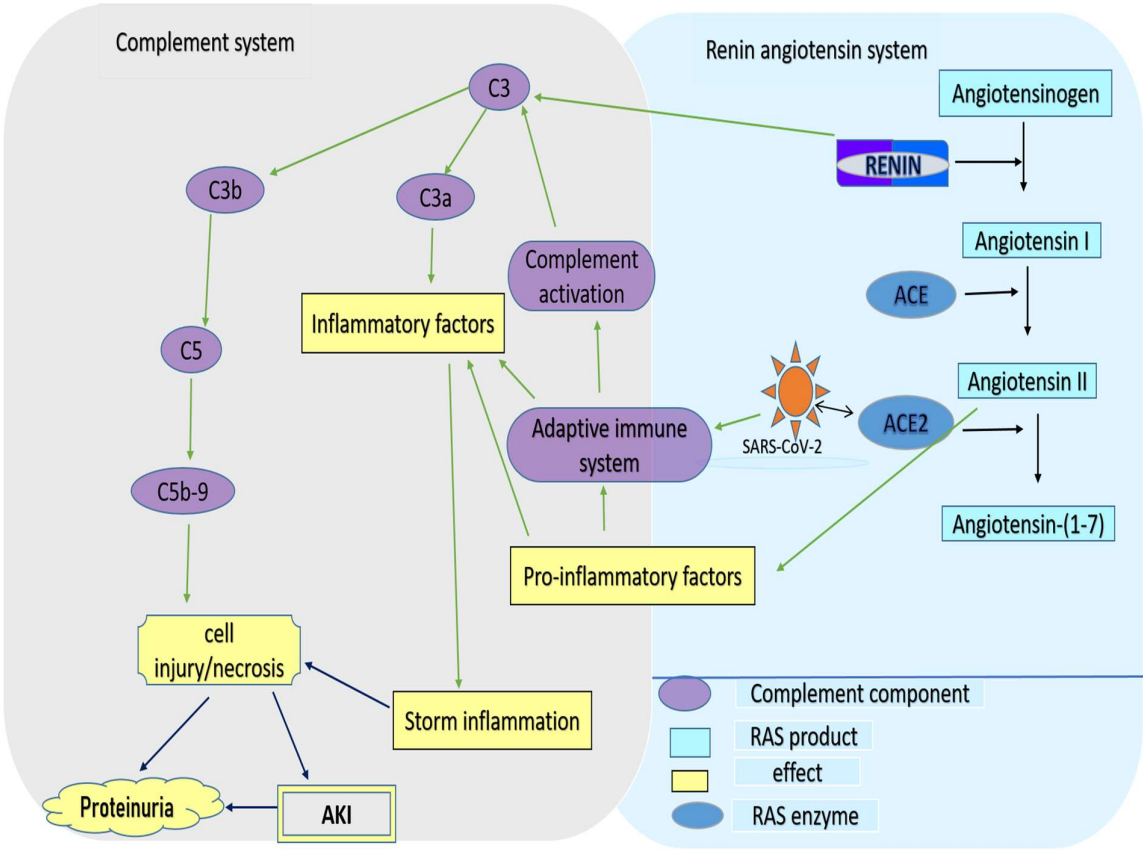
Figure 2. Interaction of RAS and immune responses.

Interaction of RAS and immune responses: SARS-CoV-2 uses ACE2 as its receptor, infected cell can trigger complement cascade activated or stimulate immune response which can recruit complement system to participate in clearing an intruder. Complement activation can be activated by renin enzyme due to positive feedback from using RAS enzyme inhibitors where all these pathways may come together to mediate storm inflammation, cell injury and multi-organ failure.

11. Conclusion and prospects

SARS-CoV-2 which causes COVID-19 binds to ACE 2 with its spikes to invade the cells. It first colonizes upper and lower respiratory. It may trigger the production of cytokines and immune responses which can affect the remaining organs where multi-organs impairment can increase morbidity and mortality. Another possibility is that circulating ACE2 can spread the virus to infect other organs apart from respiratory organs. Kidney impairment is primarily caused by indirect interactions with immune responses, but

maybe the viruses enter the kidney cells contributing to the injury, even if it is not exposed to the virus as compared to the lungs. Since its discovery, a number of studies have been done to reveal the pathogenesis of SARS-CoV-2 in different organs, where patients with critically COVID-19 exhibit a high level of pro-inflammatory mediators, which correlate with the severity of disease leading to the high mortality rate induced by AKI. Both immune response and unbalance RAS components mediated SARS-CoV-2 can promote the overstimulation of the pro-inflammatory factors which may result in organ failure, particularly kidney damage. However, several challenges have been appeared. First, the extent of acute kidney injury mediated by the immune response, viral toxicity or multifarious engagements due to SARS-CoV-2 remains uncertain. Second, the role of complement activation and its inhibitors for managing AKI and multi-organs failure during SARS-CoV-2 infection still need more clarifications. Third, the contribution of RAS to activate the cytokines production in the SARS-CoV-2 infection remains unclear. Therefore, there are many solutions to be documented in the future. Further research is needed to elucidate the mechanism of kidney impairment caused by SARS-CoV-2. To understand the mechanism and crosstalk between SARS-CoV-2, RAS, and immune response can help to establish new strategies for controlling the current threat and new emerging infection in the future.

Abbreviations

ACE2: Angiotensin converting enzyme 2
ACEIs: Angiotensin-converting enzyme inhibitors
ADE: Antibody Dependent Enhancement
AKI: Acute kidney injury
Ang II: Angiotensin II
ARBs: Angiotensin II receptor blockers
AT1/2: Angiotensin receptor type ½
AP-1: Activator Protein-1
COVID-19: Coronavirus disease 2019
CRP: C-reactive protein
DAI: DNA-dependent activator of interferon-regulatory factors
FIPV: Feline Infectious Peritonitis Virus
GSCF: Granulocyte Stimulating Colony Factor
ICAM: Intercellular Adhesion Molecule
IP-10: Interferon gamma-induced protein 10
IL: Interleukin
IRAKs: Interleukin-1 Receptor Associated Kinases
MASP-2: Mannose-binding protein-associated serine protease-2
MMP: Matrix Metalloproteinases
MAC: Membrane Attack Complex
MDA5: Melanoma Differentiation-Associated Protein 5
MERS-CoV: Middle East Respiratory Syndrome Coronavirus
MCP-1: Monocyte Chemoattractant Protein-1
MIG: Monokine induced by gamma interferon
MyD88: Myeloid Differentiation primary response 88
NADH: Nicotinamide Adenine Dinucleotide Dehydrogenase
NADPH: Nicotinamide Adenine Dinucleotide Phosphate
NO: Nitric Oxide
Nsp: nonstructural protein
NF-κB: nuclear Factor-kappa B
ORF: Open reading frame
PAMP: Pathogen-Associated Molecular Patterns
PRR: Pattern-Recognition Receptors
PHEIC: Public Health Emergency of International Concern

PTEC: Proximal Tubular Epithelial Cells
RAS: Renin Angiotensin System
RIG-I: Retinoid Acid-Inducible Gene I
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
sHLH: secondary Hemophagocytic lymphohistiocytosis
TBK1: TANK-Binding Kinase 1
TGF-β: Transforming Growth Factor –β
Th: T helper cell
TRAM: Translocating chain Associated Membrane Protein
TIR: Toll/Interleukin-1 Receptor
TMPRSS2: Transmembrane protease serine 2
TNF-α: Tumor Necrosis Factor
TLR: Toll-like receptor
TRIF: TTIR-domain-containing adapter-inducing interferon-β
VCAM-1: Vascular Cell Adhesion Molecule-1
WHO: World Health Organization

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