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COMMENT

# Targeting ACE2 as a potential prophylactic strategy against COVID-19-induced exacerbation of chronic kidney disease

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## Abstract

Patients with chronic kidney disease (CKD) are at higher risk for severe coronavirus disease 2019 (COVID-19). Such patients are more likely to develop "COVID-19-induced acute kidney injury (AKI)", which exacerbates the pre-existing CKD and increases the mortality rate of the patients. COVID-19-induced AKI is pathologically characterized by acute tubular necrosis and the interstitial infiltration of proinflammatory leukocytes. In our rat model with advanced CKD, immunohistochemistry for angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) demonstrated their strong expression in the cytoplasm of damaged proximal tubular cells and the infiltrating leukocytes within the cortical interstitium, which overlapped with the lesions of COVID-19-induced AKI. Since ACE2 and TMPRSS2 are enzymes that facilitate the viral entry into the cells and trigger the onset of cytokine storm, the renal distribution of these proteins in advanced CKD was thought to be responsible for the development of COVID-19-induced AKI. Concerning such mechanisms, the pharmacological blockade of ACE2 or the use of soluble forms of the ACE2 protein may halt the entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into host cells. This would protect against the COVID-19-induced exacerbation of pre-existing CKD by preventing the development of AKI.

**Keywords** COVID-19-induced acute kidney injury (AKI) · Chronic kidney disease (CKD) · Angiotensin-converting enzyme 2 (ACE2) · Transmembrane protease serine 2 (TMPRSS2)

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still continuing to spread around the world [1]. Currently, due to the predominance of the highly transmissible omicron variant, the number of COVID-19 patients is increasing explosively [2]. However, the omicron variant causes no symptoms or only relatively milder symptoms than conventional strains, such as sore throat, fever and runny nose, which are almost indistinguishable from those of common colds. Nevertheless, elderly people or those who have not yet been vaccinated are prone to develop severe COVID-19, featured by fatal pneumonia with acute respiratory distress syndrome (ARDS) and multiple organ dysfunction due to generalized thrombotic microangiopathy [3, 4]. Despite the recent development of novel anti-viral drugs for COVID-19 [5], the booster vaccination for the virus is currently the most effective approach to reduce the severity of the disease [6], especially for those with risk factors for developing severe illness.

In addition to underlying health conditions, such as obesity, heavy smoking and pregnancy, patients complicated with chronic diseases, such as cancer, diabetes, hypertension, cardiovascular diseases and respiratory diseases, are at higher risk of developing severe illness from COVID-19 [3, 7]. In addition, recent clinical studies revealed that chronic kidney disease (CKD) is also one of the risk factors for severe COVID-19 [8, 9]. This is because patients with CKD, which progresses relentlessly to end-stage renal disease (ESRD), already have a weakened immune system and multiple comorbid conditions, such as diabetes, hypertension and cardiovascular diseases [10]. These underlying medical conditions facilitate the invasion of SARS-CoV-2 into the body and the subsequent onset of cytokine storm, eventually causing multiple organ dysfunction in severe COVID-19 [11].

When SARS-CoV-2 enters into host cells, its spike protein binds to the host cell surface receptor,

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angiotensin-converting enzyme 2 (ACE2), which is a transmembrane protein predominantly expressed in the heart, lungs and kidneys [12]. Then, one of the transmembrane proteases of the host cells, transmembrane protease serine 2 (TMPRSS2), activates and facilitates the entry of the virus by cleaving its spike proteins. Once entering the cells, SARS-CoV-2 stimulates the production of pro-inflammatory cytokines from immune cells and triggers the onset of a cytokine storm [11]. In patients with chronic respiratory diseases or animal models of cardiovascular diseases, the expression of these proteins was increased in the pathological lesions of damaged organs, which were clinically correlated with the development of severe COVID-19 [13, 14]. On the other hand, SARS-CoV-2 infection actually altered the expression or distribution of these proteins in the heart or aerodigestive tracts, which overlapped with the lesions of COVID-19-induced organ injury [15, 16].

Using human samples or those from animal models of CKD, previous studies examined the renal expression ACE2 in some pathological conditions [17–19]. However, the results have been controversial depending on the species of experimental animals or the affected areas of the kidneys. A rat model with 5/6 nephrectomy followed by a 4–8-week recovery period was originally developed as a model of progressive glomerulosclerosis [20–22]. Later, we further revealed in our basic studies that the kidneys from rats that underwent 5/6 nephrectomy were additionally characterized by diffuse renal fibrosis after as long as a 14-week recovery period [23], and the progression of fibrosis was deeply associated with the over-proliferation of proinflammatory leukocytes [24]. In the present study, using these rats as the model of advanced CKD, we examined the histopathological features of the kidneys and the protein expression of ACE2 and TMPRSS2 at 9- or 14-week recovery period following 5/6 nephrectomy (Fig. 1). With the progression of CKD, proximal tubular cells became flattened as a result of tubular atrophy (Fig. 1Ab and c vs. a). In advanced CKD kidneys, there were numerous infiltrating leukocytes and diffuse fibrosis within the cortical interstitium (Fig. 1Ac). In sham-operated control kidneys, consistent with previous findings [25, 26], immunohistochemistry for both ACE2 (1:50; Santa Cruz Biotechnology, Inc., Dallas, TX, U.S.A.) and TMPRSS2 (1:50; Santa Cruz Biotechnology, Inc.) demonstrate positive expression in the brush border or apical membrane of proximal tubules (Fig. 1Ba and Ca). Then, with the progression of CKD, the expressions of both proteins were gradually redistributed into the cytoplasm of damaged proximal tubular cells (Fig. 1Bb and Cb). In advanced CKD, the expressions of these proteins were additionally observed in the infiltrating leukocytes within the cortical interstitium (Fig. 1Bc and Cc).

Patients with severe COVID-19 are frequently complicated with acute kidney injury (AKI), which is recognized as "COVID-19-induced (or COVID-19-associated) AKI" [27, 28]. It is caused by the direct invasion of the virus, renal hypoxia due to secondary hypoperfusion and, mainly, by generalized thrombotic microangiopathy as a result of the cytokine storm with hyper-inflammation. Therefore, the pathological features of COVID-19-induced AKI are typically characterized by acute tubular necrosis in the proximal tubules and the infiltration of proinflammatory leukocytes within the interstitium [27, 28] (Fig. 2). Among individuals

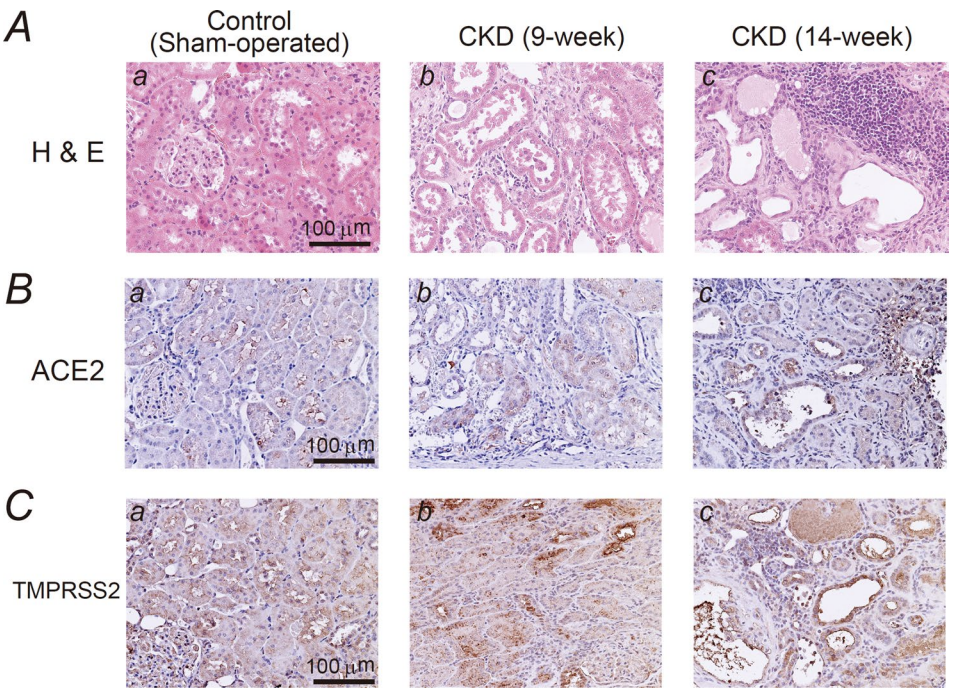


**Fig. 1** Histological features of rat kidneys with advanced chronic kidney disease (CKD) and the expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2). **A** Hematoxylin and eosin (H&E) staining in control (sham-operated; a) and advanced CKD rat kidneys at 9 weeks (b) and 14 weeks (c) after 5/6 nephrectomy. **B** Immunohistochemistry for ACE2 (brown) in control (sham-operated; a) and advanced CKD rat kidneys at 9 weeks (b) and 14 weeks (c) after 5/6 nephrectomy. **C** Immunohistochemistry for TMPRSS2 (brown) in control (sham-operated; a) and advanced CKD rat kidneys at 9 weeks (b) and 14 weeks (c) after 5/6 nephrectomy. Magnification, X20 (color figure online)

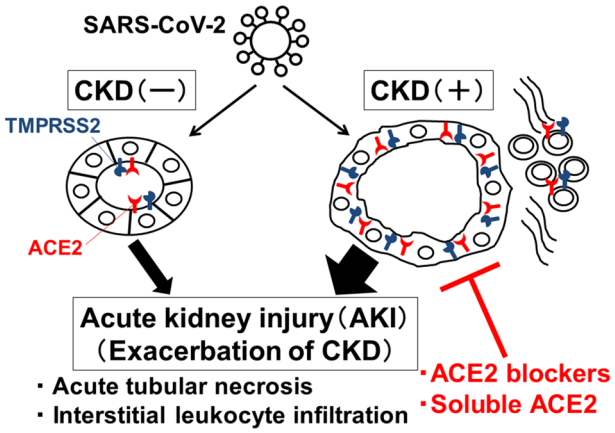


**Fig. 2** Proposed mechanisms of COVID-19-induced acute kidney injury (AKI) in chronic kidney disease (CKD). The pathological features of COVID-19-induced AKI are typically characterized by acute tubular necrosis in the proximal tubules and the infiltration of proinflammatory leukocytes within the interstitium. Among individuals infected with SARS-COV-2, those with pre-existing CKD are more likely to develop COVID-19-induced AKI than those without CKD. The renal distribution of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) in advanced CKD is responsible for the development of COVID-19-induced AKI, which exacerbates the pre-existing CKD. In addition to the pharmacological blockade of ACE2, the use of soluble forms of the ACE2 protein could prevent the development of AKI

infected with SARS-COV-2, those with pre-existing CKD are more likely to develop COVID-19-induced AKI than those without CKD [29] (Fig. 2). COVID-19-induced AKI further deteriorates the pre-existing CKD and increases the mortality rate of these patients [10, 30]. From our results, the distribution of ACE2 and TMPRSS2 in advanced CKD kidneys almost completely overlapped with the lesions of COVID-19-induced AKI (Fig. 1). Since ACE2 and TMPRSS2 are enzymes that facilitate the viral entry into the cells and trigger the onset of a cytokine storm [12], the renal distribution of these proteins in advanced CKD was thought to be responsible for the development of COVID-19-induced AKI (Fig. 2).

To reduce the risk of mortality in CKD patients, the development of AKI must be prevented [8]. Concerning the proposed mechanisms of COVID-19-induced AKI in patients with CKD (Fig. 2), targeting ACE2 would be the most useful approach. In such patients, in addition to the pharmacological blockade of ACE2 (angiotensin-converting enzyme inhibitors; ACE inhibitors or angiotensin receptor 1 blockers; ARBs), the use of soluble forms of the ACE2 protein may halt the entry of SARS-CoV-2 into host cells [31, 32]. This would protect against the COVID-19-induced exacerbation of pre-existing CKD by preventing the development of AKI (Fig. 2). In addition, suppressing the cytokine storm may also be useful, since this would ameliorate the progression of generalized thrombotic microangiopathy that causes AKI [27, 29]. In our series of patch-clamp studies, we have revealed the inhibitory properties of nonsteroidal anti-inflammatory drugs (NSAIDs), anti-hypertensive drugs, anti-cholesterol drugs and anti-allergic drugs on lymphocytes Kv1.3-channels [33–35]. Taking such pharmacological properties into account, these commonly used medications may also be beneficial in the prevention of COVID-19-induced AKI, because the channel inhibition decreases the cytokine production and thus suppresses the onset of the cytokine storm [4].

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## Declarations

**Conflict of interest** None declared.

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