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Infectious pathways of SARS-CoV-2 in renal tissue

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Coronavirus disease in 2019 (COVID-19) has spread around the world and caused significantly pandemic mobility and mortality. Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) usually infects lungs first and involves other organs including kidneys subsequently. Acute kidney injury and proteinuria in patients with COVID19 are resulted from the direct infection of the spiky-crowned viruses to proximal tubules and podocytes, leading to acute tubular injury and collapsing focal segmental glomerulosclerosis. Therefore treatment strategy should target against the direct infection of SARS-CoV2 to the renal tissue.

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Coronavirus disease in 2019 (COVID-19) is caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) (1). Followed up SARS-CoV in 2003 and Middle East respiratory syndrome-coronavirus (MERS-CoV) in 2012 (2), the coronavirus COVID-19 has affected millions of people in 212 countries/regions and caused more than a quarter-million deaths so far. It is well known that diffuse alveolar damage and acute respiratory failure are the main features of COVID-19, while multiple organ failure is very common in those non-survival patients (3, 4). It has been reported that 6.7% of patient with SARS (2003) developed acute kidney injury and the mortality of those with acute kidney injury was 91.7% (5). Compared the risk factors for mortality of patients with COVID-19, the major differences are the requirement of invasive ventilation, and developed acute cardiac and kidney injury at day 15 of hospitalization in those non-survival COVID-19 patients (6). Several cohort studies have reported that more than 5% of patients with COVID-19 developed acute kidney injury (7-9) and 43.9% of patients had proteinuria and 26.7% had hematuria on admission (9). Acute kidney injury with elevated serum creatinine and urea nitrogen,

as well as proteinuria and hematuria was an independent risk factor for patients with in-hospital mortality (9).

Infective pathways of SARS-CoV-2 have been rapidly depicted in the renal tissue over the past several months. Once the viruses flow into the renal bloodstream from the lungs, they would enter arterioles and glomerular capillaries (the first level of capillaries) (Figure 1). The glomerular endothelial cells are at the first line of defense and can be directly infected by SARS-CoV-2, identified by electron microscopy (10). The viruses are found within the cytoplasm of the glomerular endothelial cells of transplant kidneys from a 71 year-old man who had COVID-19 infection and died of multiple organ failure after 8 days in the hospital (10). The viruses, aggregated in clusters, show spiky-crown like appearance around central circular virus particle individually, with viral size up to 150 nm. Glomerular filtration barrier consists of the internal layer (50-100 nm sized endothelial fenestration and endothelium), the middle layer (glomerular basement membrane) and the external layer (slit diaphragm of foot processes extended from podocytes). Permeation of the glomerular filtration barrier for macromolecules such as albumin and immunoglobulin is mainly dependent on

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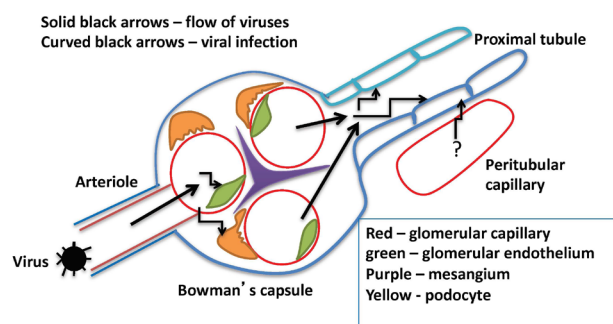


Figure 1. Schematic illustration of the infectious pathway of the coronavirus (SARS-CoV-2). SARS-CoV-2 enter arteriole and glomerular capillaries, where the viruses infect the glomerular endothelial cells first. Through the glomerular filtration barrier, the viruses can infect the podocytes, and subsequently reach the proximal tubule surface and infect the proximal tubular epithelium. It is unclear if the viruses can infect the proximal tubular epithelium via peritubular capillaries or not.

the size of the macromolecules and molecular charges, as the glomerular filtrate barrier is negatively charged (11,12). SARS-CoV-2 particles are large enough and they have to actively crawl through the three layers of glomerular filtration barrier for reaching Bowman's space. Then, SARS-CoV-2 particles are also identified in the cytoplasm of podocytes by electron microscopy, causing collapsing focal segmental glomerulopathy (13). Many viruses (up to 23 viral particles) are wrapped up by two layers of cell membranes in cytoplasmic vesicles (diameter of the vesicles is approximately 600 nm), and they are measured from 50 to 110 nm in sizes with spikes at 9–10 nm (13). Almost simultaneously, two other case reports also describe the development of collapsing focal segmental glomerulopathy in two patients positive for COVID-19, leading to renal failure and nephrotic proteinuria, but no viral identification by electron microscopy is mentioned (14,15). From Bowman's space, SARS-CoV-2 particles easily flow into proximal tubules where they enter angiotensin converting enzyme 2 (ACE-2) rich tubular epithelium (Figure 1). Several studies find clusters of SARS-CoV-2 particles individually or wrapped by cell membranes in the cytoplasm of proximal tubules as evidence of direct viral infection (16,17). Su et al report that the viral particles are wrapped up by double-membrane vesicles, and are measured from 65 to 136 nm in sizes with surrounded spikes ranged from 20 to 25 nm (16). The authors mainly identify the viral particles in proximal tubules contributing to renal failure, but also see the viruses in podocytes and distal tubules. Furthermore, they confirm the infected proximal tubules by the viruses using immunofluorescent method. Farkash et al report that the viral sizes ranged from 65 to 91 nm in

the cytoplasm of proximal tubules, which direct infection is most likely related to the renal failure of the 51 year-old man who contracted with COVID infection and developed multi-organ failure (17).

ACE2 are widely distributed in the body including in lungs, heart, endothelial cells, podocytes and renal tubular epithelium etc, and are considered the major receptors for SARS-CoV-2 to enter cells (18,19). It is reported that coronaviruses enter cells via endocytosis (20), which is further supported by the finding of SARS-CoV-2 wrapped by double layers of intra-cytoplasmic vesicles in several recent studies (10,13,16,17). But no study has demonstrated the viral infection into nuclei morphologically. In summary, SARS-CoV-2 can directly infect glomerular endothelium, podocytes and renal tubules, causing dominant findings of acute tubular injury and occasionally collapsing focal segmental glomerulopathy in the kidney tissue.

Authors' contribution

WY prepared the clinical aspect of the manuscript and PZ prepared the pathology aspect of the manuscript.

Conflicts of interest

The authors report no conflict of interest.

Ethical considerations

Ethical issues include plagiarism, double publication, and redundancy have been completely observed by the authors.

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