Expression of CD147 and Cyclophilin A in Kidneys of Patients with COVID-19

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Coronavirus disease 2019 (COVID-19), a novel illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), broke out in December 2019 in Wuhan and soon propagated rapidly to the whole world. Although several reports have addressed the clinical and pathologic abnormalities of the kidney in patients with COVID-19, there are still many uncertainties that exist, especially about the direct invasion or virulence of SARS-CoV-2 to kidney resident cells.

Previously, we reported the presentation of coronavirus-like particles in tubular epithelial cells and podocytes, which is potentially or partially relevant to AKI and proteinuria (1). For the viral invasion, the first step is the binding of the virion spike protein to its receptors on the host cells. In this regard, angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 are two well-identified receptors for SARS-CoV-2 and Middle East Respiratory Syndrome Coronavirus, respectively. Currently, for the receptors of SARS-CoV-2, there are several candidates proposed, among which ACE2 is most popular. Other than ACE2, CD147 is another alternative receptor for SARS-CoV-2. It is well documented that CD147 facilitates HIV-1, vaccinia virus, measles virus, and malaria parasitic invasion, and targeting CD147 is proposed to be a promising strategy to prevent the infection of pathogens (2).

Here, we evaluated the kidney expression of CD147 via immunohistochemistry in 11 deceased patients with COVID-19, as well as three non–COVID-19 autopsied samples (autopsied control). Meanwhile, preimplantation kidney samples from a deceased donor with acute tubular injury (ATI) were included as non–COVID-19 AKI control. Another six biopsied samples from patients without diagnostic morphologic abnormalities were adopted as non-AKI controls. We found that in non-AKI control samples, CD147 primarily expressed on the basolateral membrane of tubular epithelia without detectable glomerular staining (Figure 1A). However, in autopsied tissue (Figure 1B) and kidney donors (Figure 1C) with ATI that had strictly ruled out COVID-19, the tubular epithelial expression of CD147 altered with an additional intercellular junction distribution. More strikingly, in patients with COVID-19, the distribution of CD147 expanded from the basolateral to circumferential pattern, including interfacial and apical sides (Figure 1D), which postulates the potential role of tubular CD147 in COVID-19, especially that its apical presentation likely contributes to the putative invasion of SARS-CoV-2 from that lumen side into the cytoplasm of tubular epithelial cells. Also, a few CD147-positive podocytes and parietal cells were observed in COVID-19 (Figure 1E).

There are diverse extracellular, membranous, and intracellular chaperones of CD147 that have been identified, among which cyclophilin A (CypA) is the most well studied and acts as an extracellular and intracellular chaperon of CD147 synchronously (3). Circulating or extracellular CypA is an essential interactor to bridge pathogens with CD147 for the following endocytosis of the virus, including SARS-CoV-2, HIV-1, cytomegalovirus, Neisseria meningitidis, and Plasmodium. Blocking CD147 or CypA is efficient to prevent the entry of these microorganisms. More interestingly, CypA is also an important intracellular partner of CD147, which plays pivotal roles in T cell activation and coronavirus replication as well (4). By immunostaining from the same samples as we described above, we found that the expression of CypA in non-AKI biopsied samples (Figure 1F) and non–COVID-19 autopsied tissue with ATI (Figure 1G) was rather low; however, it was enhanced in tubular epithelia as well as in podocytes and parietal cells in COVID-19 (Figure 1H and I). It is well accepted that CypA plays a suppressive role in CD4+ T cell development; therefore, we propose that the upregulated CypA may contribute a lot to the conspicuous lymphocytopenia in patients with COVID-19. Moreover, the upregulation of CD147-CypA in the podocyte from patients with COVID-19 in our study is consistent with previous reported podocyte injury in patients with COVID-19 and in vitro experiments.

A specific inhibitor of CypA, cyclosporin (CsA), is commonly prescribed as an immunosuppressant to patients with allograft or autoimmune diseases. Thus, at the beginning of the epidemic of COVID-19, we were especially worried about this immunocompromised population. Notwithstanding, until now, there is no convincing evidence to show the enhanced risk of SARS-CoV-2 infection in patients who are under immunosuppressive therapies. In a systematic review, tacrolimus, one of the calcineurin inhibitors like CsA, showed beneficial effect on the course of SARS-CoV-2 (5). In addition, CsA and tacrolimus are confirmed to inhibit the infection of coronaviruses by several in vitro and in vivo studies. Thus, there is no validated evidence to infer the necessity.
to discontinue these immunosuppressants in treated patients. In addition, potential application of the CypA inhibitors, especially the second generation of CsA analogs that do bind CypA without immunosuppression, is promising in viral infection.

Taken together, our findings suggest that the CD147-CypA axis potentially participates in the pathogenesis of kidney injury in patients with COVID-19. Last but not least, although less significant, the alteration of CD147-CypA expression in the kidney donor before this pandemic prompts us to carry out further studies of it in diverse kidney diseases.

Disclosures
All authors have nothing to disclose.

Funding
This work was financially supported by National Natural Science Foundation of China grants 81873602, 8196138007, 81974096, 81770711, and 81570671; National Key Research and Development Program grants 2018YFC1314000, 2020YFC0845800, and 2020YFC0844700; and the Program for Huazhong University of Science and Technology Academic Frontier Youth Team grant 2017QYTD20.

Acknowledgments
H. Su and C. Zhang conceived and designed the study; F. Tang, L.-X. Yi, and H.-Y. Zhu performed the experiments; Y. Gao, Y.-C. Li, C. Wan, and Z.-D. Wang collected and analyzed the data; H. Su drafted the manuscript; C. Zhang revised the manuscript; and all authors revised the manuscript critically for important intellectual content and gave final approval of the version to be published.

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Published online ahead of print. Publication date available at www.cjasn.org.