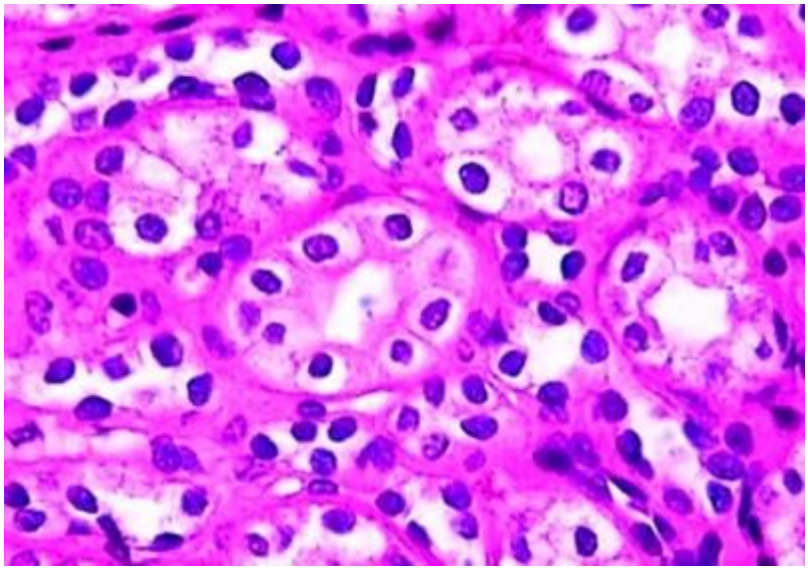
Coronavirus disease 2019 (COVID-19) is a clinical syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is a systemic multiple-organ disease characterized by a broad spectrum of clinical manifestations, including a high vulnerability of kidneys to SARS-CoV-2. A high incidence of acute kidney injury and a strong correlation between renal dysfunction and high mortality were reported in acute COVID-19 patients. Viruses were detected in the kidneys, especially in renal epithelial cells. In this study, the Chinese researchers investigated whether SARS-CoV-2 binds to kidney injury molecule-1 (KIM1), which is drastically upregulated in the apical membrane of the proximal tubule only upon kidney injury.

KIM1 is a type-1 transmembrane protein, which consists of the immunoglobulin variable Ig-like (IgV), mucin, transmembrane and cytosolic domains. Previous studies on Ebola and Dengue viruses have demonstrated that the IgV domain of KIM1 is required for virus binding and internalization.

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein. The S protein appears to be a major pathogenic factor contributing to the unique pathogenesis of SARS-CoV-2. The S protein is a glycosylated homotrimer with each monomer composed of subunits S1 and S2, separated by host cell proteases. The S1 domain comprises the N-terminal domain (NTD), the receptor binding domain (RBD) with a receptor binding motif (RBM), and two C-terminal domains. The RBD in the S1 subunit is a short immunogenic fragment that facilitates the S protein binding to the host cell angiotensin-converting enzyme 2 receptor (ACE2).

ACE2 is enriched in the kidney as the target for SARS-CoV2, but, the authors speculated that additional receptors may mediate the renal infection. The co-expression of KIM1 and ACE2 in the kidney, colon, rectum, testis, and gallbladder, all of which are the target organs of SARS-CoV-2, suggests a close association between KIM1 and COVID-19 manifestations.



Results

The results revealed that the RBD of the SARS-CoV-2 S protein binds to KIM1 and that the immunoglobulin variable Ig-like (IgV) domain of KIM1 plays a key role in this recognition.

Interstingly, compared to SARS-CoV-RBD and MERS-COV-RBD, SARS-CoV-2-RBD displayed the highest binding affinity to KIM1, although SARS-CoV-RBD and SARS-CoV-2-RBD target the same binding pocket in the IgV domain.

Fluorescein isothiocyanate labeling, used to track SARS-CoV-2-RBD in human cells, showed a reduced binding signal on the surface of human renal cells when KIM1 was knocked out, and a more intense signal when KIM1 was overexpressed. The restoration of full-length KIM1 and overexpression of IgV restored the binding signal on the surface of human renal cells. These data confirmed the crucial role of the KIM1 IgV domain in SARS-CoV-2 attachment.

The interaction between SARS-CoV-2 RBD and KIM1 was confirmed by coimmunoprecipitation assay, fluorescence spectrophotometry, and confocal microscopy. Knocking out KIM1 or deleting the IgV domain abolished the binding between KIM1 and SARS-CoV-2 RBD. Similarly, antagonist peptide AP2, which competitively binds with SARS-CoV-2 RBD, inhibited the interaction between SARS-CoV-2 RBD and KIM1. These findings also confirmed the crucial role of the KIM1 IgV domain in mediating the interaction between

KIM1 and SARS-CoV-2.

The interaction of SARS-CoV-2 RBD with KIM1 IgV resulted in a combined binding free energy of −35.64 kcal/mol, which is lower than that of SARS-CoV-2 RBD and ACE2 (−50.60 kcal/mol).

According to the authors, the SARS-CoV-2 RBD binds to KIM1 and ACE2 by distinct binding regions. This suggests that KIM1 and ACE2 may synergistically mediate the invasion of SARS-CoV-2.

Conclusion

This study has shown that KIM1, which is not normally present but is highly expressed in the apical membrane of the proximal tubule only upon kidney injury, has a significant role in the renal tropism of SARS-CoV-2. Compared to SARS-CoV RBD and MERS-COV RBD, SARS-CoV-2 RBD showed the highest binding affinity for KIM1. The findings revealed the crucial role of the KIM1 IgV domain in mediating the interaction between KIM1 and SARS-CoV-2.

The authors proposed a “vicious cycle” model, which may explain the renal tropism of SARS-CoV-2 in COVID-19 patients. During the initial stage of SARS-CoV-2 invasion, ACE2 is the primary target because of its higher physiological level and binding affinity. However, after the acute kidney injury caused by the virus and significant upregulation of KIM1, the ACE2, and KIM1 may synergistically mediate SARS-CoV-2 invasion and rapidly promote the infection. Consequently, this “vicious cycle” further exacerbates a kidney injury.

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