Receptor-Recognition Mechanism of the Newly Emergent Coronavirus MERS-CoV Determined

The newly-emerged coronavirus, named the Middle East respiratory syndrome coronavirus (MERS-CoV), is highly pathogenic. Patients suffer severe pulmonary diseases, including fever, cough, and an acute respiratory distress syndrome. In some cases, the disease course is accompanied by renal failure, leading to severely high mortality.

As of July 11th 2013, a total of 81 laboratory-confirmed infection cases, including 45 deaths, had been reported globally. Since the first case-report in Saudi Arabia last year, MERS-CoV has now spread to affect multiple countries in the Middle East, Europe and North Africa. In addition, there has been accumulating evidence showing the limited local transmission of the virus among close contacts. Consequently, people are worried of a second potential coronavirus pandemic ten years after the SARS outbreak. To combat this virus, it is urgent to illustrate how the virus infects humans.

MERS-CoV belongs to the *Betacoronavirus* genus in the *Coronaviridae* family. As with other coronaviruses, MERS-CoV utilizes the surface spike protein for receptor recognition. The specific binding of the viral spike to the cellular receptor mediates the attachment of viruses to host cells, which is a crucial step initiating infection.

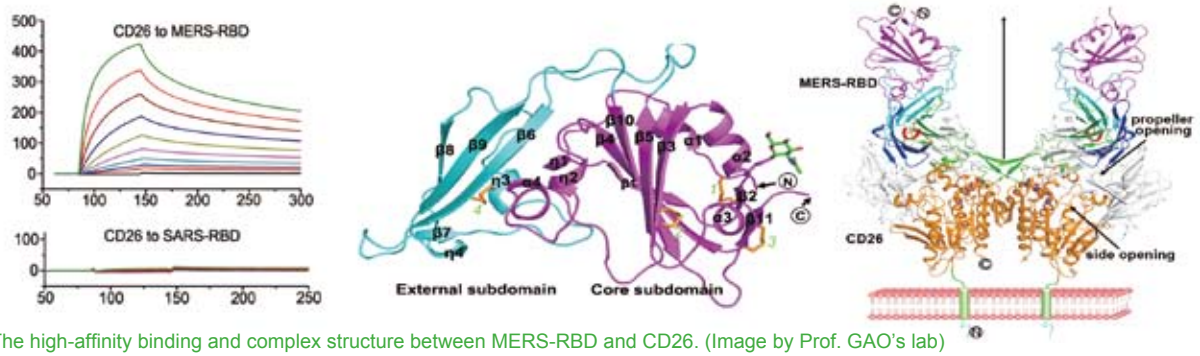
Recently, CD26 (also known as dipeptidyl peptidase 4, DDP4) was identified as the functional receptor for MERS-CoV. The molecular mechanism of CD26 recognition by the novel coronavirus, however, remains elusive. This is a key question regarding the viral pathogenesis and would be meaningful to the development of anti-viral drugs targeting the viral entry process.

One division of Prof. GAO Fu (George F. Gao)'s laboratory at the Institute of Microbiology, CAS is focused on the mechanisms of viral cross-species transmission and immune recognition. To delineate the receptor-recognition basis of MERS-CoV, related structural and functional studies were swiftly started in the laboratory. Prof. GAO and his colleagues first identified the spike region that is responsible for receptor-engagement. This spike region is denoted the receptor binding domain of MERS (MERS-RBD) which exhibits a high and specific binding-avidity for human CD26. Then, free MERS-RBD protein and its complex with CD26 were abundantly prepared, and successfully crystallized.

The viral RBD is composed of a core subdomain and an external receptor-binding motif. The former is homologous to that of the SARS-CoV spike protein, while the latter is a novel strand-rich unit which recognizes blades IV and V of CD26 *β*-propeller. The receptor itself is a type II transmembrane protein, presented on cell surface as homodimers. MERS-RBD locates at the membrane-distal tip of the receptor dimer, forming an overall "angel-wing"-like structure (Figure).

Detailed analysis revealed that the RBD/CD26 interaction is mainly mediated by salt-bridges and hydrogen-bond contacts among hydrophilic residues at the binding interface. The emergence of MERS-CoV infections poses a severe threat to public health worldwide. The viral entry process represents one of the best drug targets. The identification of key residues, via high-resolution structures, mediating the attachment of MERS-CoV to CD26 could direct future anti-viral research.

This study elucidates the receptor-recognition mechanism of MERS-CoV and would facilitate rational design of both anti-viral drugs and prophylactic vaccines. These results were published online in *Nature*.



The high-affinity binding and complex structure between MERS-RBD and CD26. (Image by Prof. GAO's lab)