Molecular Mechanisms Of COVID-19

Fang Li[1]

[1]***University of Minnesota***

lifang@umn.edu

The SARS-CoV-2 virus causes the COVID-19 global pandemic. How does the virus remain highly infectious while escaping the immune surveillance effectively? We compared the human receptor binding affinity and cell entry mechanism of the SARS-CoV-1 virus and SARS-CoV-2 virus to reveal the mystery. To this end, we determined the crystal structures of the receptor-binding domains (RBDs) of both SARS-CoV-1 and SARS-CoV-2 each complexed with their receptor human ACE2. We demonstrated that SARS-CoV-2 RBD has a higher affinity for human ACE2 than does SARS-CoV-1 RBD. Moreover, We determined the cryo-EM structure of SARS-CoV-2 spike protein, revealing that SARS-CoV-2 RBD is frequently embedded in the spike protein and hence escaping the host immune surveillance. In contrast, SARS-CoV-1 RBD is constantly exposed on the tip of the spike protein and ready to bind the human ACE2. Furthermore, we discovered that cell entry of SARS-CoV-2 can be enhanced through proteolytical activation by the human proprotein convertase furin. Overall, we have discovered three key molecular features of cell entry mechanisms of SARS-CoV-2: high receptor-binding affinity of its RBD, immune evasion of its spike protein through frequently hidden RBD, and furin activiation of its spike protein. These molecular mechanisms of SARS-CoV-2 are critical determinants of the COVID-19 pandemic and guide developments of vaccines and therapeutics.