The current dominant SARS-CoV-2 variant Omicron BA.2 has spread globally within only two months. Recent works published in Cell Research and Science reveal the molecular basis of increased transmissibility of Omicron BA.1 and BA.2 and their possible mouse origin.

SARS-CoV-2 Omicron variant with an unprecedented high rate of mutations and transmissibility has swept the world during the past several months. The high prevalence of Omicron can be attributed to their resistance to most clinically approved neutralizing antibodies, striking immune evasion from the humoral immunity elicited by the current COVID-19 vaccines and higher transmissibility rates. Understanding the structural and functional basis of the increased transmissibility and the origin of Omicron would provide insights into developing countermeasures against the COVID-19 pandemic.

Most recently, Yin, Xu and colleagues have reported in Science4 and Cell Research3 the cryo-EM structures of Omicron BA.1/BA.2 spike trimer in complex with human angiotensin-converting enzyme 2 (hACE2) (Fig. 1a). Structurally, the Omicron receptor-binding domain (RBD) adopts two conformations, up and down. Only the “up” RBD exposes the receptor-binding site. They firstly observed an RBD (up)–RBD (down) interaction for the BA.1 and BA.2, which was not found in the wild-type (WT) spike trimer previously. The up–down RBD dimer stabilizes the up conformation of one RBD and thus promotes hACE2 binding, leading to higher affinity of Omicron RBD to hACE2 compared to that of WT. The newly discovered up–down RBD dimer may be a good target for developing therapeutics or vaccines. Therefore, it would be interesting to explore whether the RBD dimer is a good conformational immunogen to induce more broad or potent neutralizing antibodies. Moreover, two or three RBDs bind at least two hACE2 molecules for BA.2. By contrast, only one RBD in open conformation was observed to bind one hACE2 molecule for BA.1. This discovery seems to explain the stronger hACE2-binding capacity of BA.2 than that of BA.1 (Fig. 1a). The Omicron RBD is more dynamic than WT RBD. It will also be constructive to determine whether stabilizing the RBD in unique states such as all down or all up would increase the breadth of the neutralizing antibody.

Atomic model of hACE2-bound Omicron RBD revealed that K417N loses a salt bridge with hACE2 D30, while Q493R and Q498R form two new salt bridges with E35 and D38 of hACE2, resulting in a net enhanced binding capacity of BA.1/BA.2 to hACE2, which was consistent with a previous study.8 These results elucidate why the BA.1/BA.2 retains efficient receptor engagement, while harboring many mutations. However, decreased binding activities were observed for BA.4/BA.5 by other research group due to substitutions of F486V and R493Q, which might hinder the speed of BA.4/BA.5 spreading.9 The authors also found that Omicron BA.2 exhibited the highest binding capacity to hACE2, with 2-fold and 11-fold higher than those of BA.1 and WT, respectively (Fig. 1b). Furthermore, BA.2 exhibited higher stability than BA.1 due to the intermolecular hydrogen bond formed by N405 and R403 (Fig. 1b). The higher stability and hACE2-binding capacity of BA.2 relative to BA.1 might be the reason why BA.2 has gradually replaced BA.1 sublineage.

A novel epitope targeted by the BA.1/BA.2 neutralizing antibody JMB2002 was reported by the authors (Fig. 1c). However, JMB2002 could not neutralize Delta due to the substitution of L452R. Delta may make a comeback in the future. Moreover, the BA.4/BA.5 also exhibits the L452R substitution. Developing a bispecific neutralizing antibody targeting the epitope of JMB2002 and another highly conserved region such as sarbecovirus epitope may be an alternative for broadly combating multiple SARS-CoV-2 variants. However, since the S1 containing main neutralizing epitopes is under high mutation pressure, it is difficult to develop S1-specific broad-spectrum therapeutics. To combat SARS-CoV-2 variants, drugs targeting the conserved S2 region such as HR1 and HR2 need to be developed. For example, peptides EK1 and EK1C4 targeting HR1 have shown efficacy as pan-coronavirus inhibitors against the current SARS-CoV-2 variants.7

The evolution of Omicron is independent of all previous SARS-CoV-2 variants. The Omicron RBD can effectively bind to mouse ACE2 (mACE2), while other variants, such as Alpha and Beta only weakly bind mACE2.4,8 Xu, Yin and colleagues further elucidated the cryo-EM structures and molecular interactions between BA.1/BA.2 and mACE2 (Fig. 1d). The substitutions of Q493R, Q498R, and N501Y in the Omicron RBD play an essential role in enabling efficient mACE2 binding. Notably, several mouse-adapted strains reported contain these mutations, such as MASCp69 (N501Y), MA1010 (Q493K), and WBP-11 (Q493K and Q498H). Since cats are susceptible to SARS-CoV-2, the authors speculate that the virus from humans or cats might be passed to mice and evolve to Omicron (Fig. 1e). WT or other variants might infect aged mice firstly because aged mice are more susceptible to SARS-CoV-2, and mutations like those mentioned above occurred in the virus after several passages, leading to infection in young adult mice and finally evolving into Omicron. Whether mouse is the origin of Omicron remains to be further investigated. Nevertheless, the idea of potential animal hosts, such as minks, pangolins, cats, dogs and...
other wild animals, is alarmingly plausible. Accordingly, the surveillance of SARS-CoV-2 mutations in these hosts needs to be continuously performed.

In summary, the findings from Xu, Yin and colleagues shed light on the mechanism of high transmissibility and the possible mouse origin of Omicron, which should pave the way for designing a preventive strategy across the spectrum of coronavirus mutations and, correspondingly, developing broad-spectrum vaccines and drugs against SARS-CoV-2 and its variants.

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ADDITIONAL INFORMATION

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