

Reverse spillover of SARS-CoV-2 from human to wild animals

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The heavily transmitted and mutated SARS-CoV-2 has constituted a sustained threat to global health. A recent article published in *Nature*, firstly provided solid evidence confirming the cross-species transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from human to free-ranging white-tailed deer (Hale et al., 2022). More importantly, circulation of SARS-CoV-2 among deer rapidly resulted into new phylogenetic clades of deer-only viruses which were believed linking to the high infection rate of SARS-CoV-2 within white-tailed deer in northeast Ohio, USA (Hale et al., 2022).

In this study, by integrating epidemiological information, surveillance data, and the whole-genome sequencing data on the human-animal interface, human-to-deer transmission of SARS-CoV-2 was confirmed (Hale et al., 2022). Moreover, new deer-specific lineages in the following intra-species transmission were dominantly detected in wild white-tailed deer (Hale et al., 2022). These evidences firstly demonstrated the SARS-CoV-2 transmissivity in wildlife, meanwhile, also implied the possibility of a new evolution pathway of SARS-CoV-2 within a potential animal reservoir. In addition, the cross-species transmission of SARS-CoV-2 was not only observed in wildlife, but also in domestic and experimental animals which alerted for a broader surveillance (Shi et al., 2020; Xiang et al., 2022). Although spillback to human was not reported in this study, previous publication has observed the transmission between human and mink (Oude Munnink et al., 2021). Moreover, we also successfully generated a

mouse-adapted SARS-CoV-2 strain only after six passages since the first intranasal inoculation, which suggested its distinct capability of rapid adaption within hosts (Gu et al., 2020) (Figure 1).

Mechanically, evolution of SARS-CoV-2 results in accumulation of nucleotide or amino acid substitutions, which presumably leads to the faster spread of SARS-CoV-2 among susceptible species or adaption to new hosts. In this study, a few clade-defining amino acid mutants which were identified in all deer viruses were rarely relative to human SARS-CoV-2 after deer-to-deer transmission (Hale et al., 2022). Notably, the affinity of a receptor binding domain (RBD) of viral spike protein to host angiotensin converting enzyme 2 (ACE2) promoted virus entry, consequently determined virus infectivity and pathogenicity. Therefore, amino acids substitutions in RBD are critical for SARS-CoV-2 evolution and species-transmission. Studies have reported that a fitness-enhancing mutant D614G in RBD motif enhances its binding to human ACE2, which largely increases SARS-CoV-2 transmissibility among human (Zhou et al., 2021). Following the global circulation, later-emergent variants of concern (VOC) strains defined by WHO, named Alpha, Beta, Gamma, Delta and the latest appeared Omicron, showed more accumulated mutants in RBD domain, which gradually enhanced binding affinity to hACE2, consequently weakened the neutralizing antibody activity obtained from previous infection or vaccination. For incidence, published data identified the N501Y in Alpha, Beta and Gamma, E484K in Beta and Gamma, L452R, T478K in Delta as key substitutions leading to their fast worldwide spread. Especially, Omicron presented more

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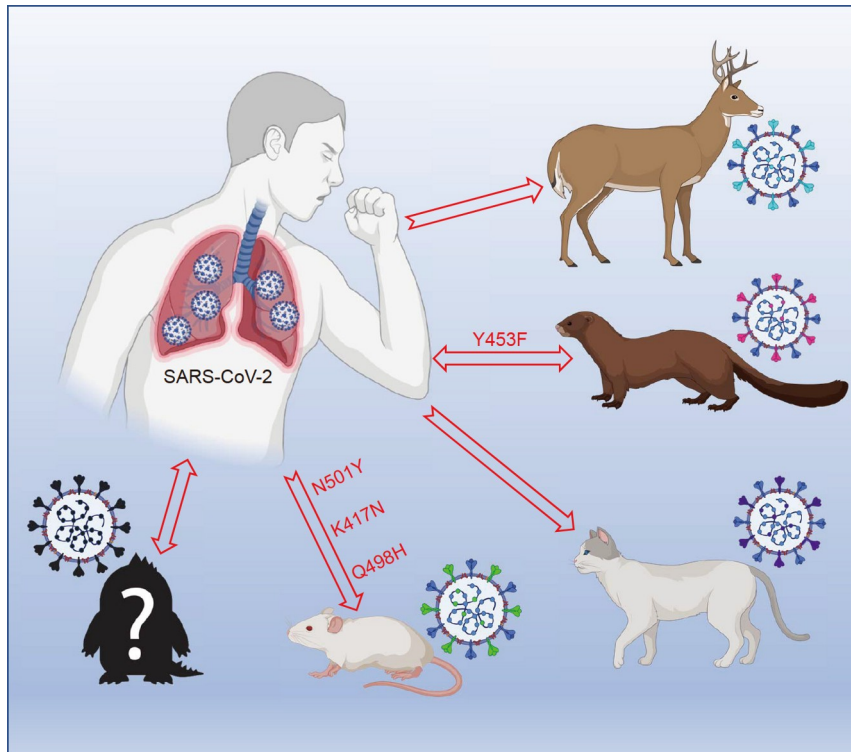


Figure 1 Constant evolution of SARS-CoV-2 results in its cross-species transmission. Key amino acid substitution(s), especially in RBD, have been proved to play an important roles in SARS-CoV-2 evolution and species-transmission. Items used in this figure are created with BioRender.com.

amino acids substitutions at RBD domain, which enhanced its binding to hACE2, likely increased the transmission. Like its evolution within human, recent studies demonstrated that mutant(s) in RBD also contributed to initiating an evolution pathway in newly susceptible species. In this study, E484D in RBD motif, detected in singleton deer viruses, was rare in human viruses and presented less sensitivity to human convalescent sera neutralization (Hale et al., 2022). This mutant, thus, is believed to be induced during viral circulation among deer and may play an important role in deer-to-deer transmission. Moreover, some substitutions within RBD motif were identified to embow RBD's binding capability both to human and other species, therefore, implied a risk of SARS-CoV-2 transmission jumping back to human. For instance, Y453F substitution was proved to largely enhance virus affinity to mink ACE2, meanwhile retained its binding to hACE2, resulted in the adaption to mink host, and the spillback to human (Ren et al., 2021). In addition, Recent studies using deep sequencing for mouse adapted strains revealed that mutations, like N501Y, K417N and Q498H in RBD were also observed in human VOC strains, which contributed to the increasing virulence and circulation of SARS-CoV-2 both in mice and human (Gu et al., 2020; Wang et al., 2020; Sun et al., 2021). Based on cumulative solid evidence consolidating continuous cross-transmission of SARS-CoV-2 during the latest

three years, more and more scientists believed that SARS-CoV-2 was the result of multi-step natural evolution and selection, rather than a sudden evolution in urban market or even a product generated in a laboratory (Wu et al., 2021). Altogether, constant evolution of SARS-CoV-2, especially mutant(s) in RBD leads to the cross-species jump of SARS-CoV-2 from human to previously reported hosts, or worse, causes further spillback or unknown cross-species transmissions.

There is no doubt that global phenomena such as urbanization and international travel have accelerated the worldwide expansion of pathogens, like SARS-CoV-2. Attributing to the advanced sequencing techniques and unprecedented online data sharing platforms such as GISAID, Nextstrain and Pango, we have the capability to do a real-time surveillance of any newly appeared epidemic. Investigation of SARS-CoV-2 in white-tailed deer confirmed the sustaining transmission of SARS-CoV-2 in nature which emphasized the importance of border surveillance. Therefore, more actions, like the "One health" program should be urgently advocated and executed to monitor human neighbours including domestic animals, as well as wildlife which become closer to human during the rapid urbanization era. It's still need our endeavours to do more pre-emergent operations at least but not limited to enhanced biosecurity, early warning, and immediate culling of infected animals.

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