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Letter to the Editor

The novel hamster-adapted SARS-CoV-2 Delta variant may be selectively advantaged in humans

We have previously reported on the importance of the structural dynamic of SARS-CoV-2 variants for risk assessment [1]. The same applies in the case of the hamster-adapted Delta variant recently described in Hong Kong [2,3]. On January 18, 2022, the Hong Kong sanitary authorities ordered the culling of hamsters, closed pet-shops and sent pet-shop visitors into quarantine after hamsters sold at a local store were found infected with the Delta variant of SARS-CoV-2 [2,3]. This variant initially infected an employee and a customer and further human-to-human transmission was evidenced [2,3]. This is reminiscent of what happened in Denmark with the SARS-CoV-2 outbreak in farmed minks which infected humans back [4,5]. At that time, Denmark culled all minks on fear that the mutations observed in mink-adapted viruses might impair the mass vaccination process [6]. However, although no human-to-human transmission occurred in Denmark, this happened in Hong Kong raising the question of the risk posed by this hamster-adapted SARS-CoV-2 variant. A series of specific mutations were found, when compared to the Delta variant, in viruses isolated from both humans and hamsters [2]. Three mutations were located in the Spike protein. Two of the mutations, L18F and H49Y, were located in the N-terminal domain and could be involved in the binding of NTD-specific antibodies and viral entry, respectively [2]. The third one, D427G, was located inside the Receptor Binding Domain (RBD) but outside the Receptor Binding Motive (RBM) which interacts directly with the ACE2 receptor. The last hamster-derived mutation, T38I was located in ORF10. The effect of the D427G mutation was analyzed by in-silico analyses with Hyperchem (http://www.hypercubeusa.com), Deep View/Swiss-Pdb viewer (https://spdbv.vital-it.ch) and Molegro Molecular viewer (http://molexus.io/molegro-molecular-viewer) as previously described [1], using as a reference the ACE-2 RBD complex obtained from pdb 6M0J (B.1 Wuhan strain). A source file was generated for both human and hamster ACE-2. The affinity of SARS-CoV-2 mutants for human and hamster ACE2 was estimated by energy minimization of the complex after introducing the appropriate mutations as previously described [1]. Analyzing, the impact of the D427G mutation using 3D modeling shows that although not directly involved in the interaction with ACE2, it has a major positive influence on the affinity in both hamsters and humans. The complex between human ACE-2 and the receptor binding domain (RBD) of the Delta spike protein is stabilized by several tight contacts between both partners. Among these contacts, the H-bond between the RBD residue Y453 and H34 (human ACE-2) is especially important because it occupies a central position in the complex (Fig. 1 upper panel). In the hamster ACE2 protein, H34 is replaced by Q34 (Fig. 1 upper panel). The flexibility of the side chain of Q34 still allows the formation of a H-bond with Y453, yet at the price of a torsion which rejects the amide group of Q34 on the opposite position of H34. This conformational conflict is annihilated by the mutation D427G. Initially, the carboxylate group of D427 forms a H-bond with G413. This interaction rigidifies the regions of the RBD located between G413 and Y453, so that N422, located in a short α-helix underneath Y453, does not physically interact with Y453. The D427G mutation breaks this H-bond, transforming the α-helix into a more flexible loop and eventually allowing N422 to interact with the aromatic ring of Y453 through a NH-π interaction (Fig. 1 lower panel). The consequence is that Y453 is slightly attracted by the RBD, leaving more room for Q34 whose side chain can now move in the initial orientation of H34, which further stabilizes the H-bond between Y453 and Q34. This translates into a reduction of the distance with the ACE2 Q34 from 2.7 Å to 1.6 Å for D427 and G427, respectively (Fig. 1 upper panel). When the D427G-virus infects humans back, this conformational advantage is still operative, so that the H-bond between Y453 and H34 is also optimized. It moves from 3.5 Å to 2.2 Å for D427 and G427, respectively (Fig. 1 upper panel). Another important contribution to the energy of interaction of the complex is F486 (located in the RBD) which stacks onto the aromatic ring of Y83 (ACE2), with a ΔG value of −31.5 kJ/mol-1. When the Delta variant RBD binds to hamster ACE-2, this stacking becomes suboptimal, due to a slight shift of F486 (ΔG = - 27.9 kJ/mol-1, which represents a loss of affinity of 11.4% for this residue). The long-range conformational change induced by the D427G mutation slightly moves the aromatic ring of F486 and restores the initial energy of interaction (G = - 31.4 kJ/mol-1).

These results indicate that the question of the risk of expansion of the hamster-adapted SARS-CoV-2 Delta variant in the human population is valid. Other species than humans can be infected by SARS-CoV-2, such as minks, hamsters, cats, tigers or dogs [7,8]. These wild and domestic animals present also a virtual risk of infecting humans back with a mutated SARS-CoV-2. Like other RNA viruses, SARS-CoV-2 is evolving through a quasispecies mechanism [9], allowing the generation of post-infection mutations under positive selective pressure, i.e. host-driven, to improve affinity for the receptor and/or to escape immune response. This correspond to what has been described on hamsters [2,3]. However, in this case these mutations appear to be also more favorable for the virus on humans. This hamster-adapted delta variant is thus potentially selectively advantaged when infecting the human population back and may thus have also the potential for becoming a future pandemic variant. However, this is not straightforward. The emergence of an infectious disease is a stochastic process and many things may happen from the elimination of the variant to the emergence of a pandemic. This process of disease emergence is society-driven [10] and if a virus, even with a potentially selective advantage, does not meet the proper societal environment, it will not emergence as a pandemic variant. It is thus not currently possible to predict what will happen with this hamster-adapted

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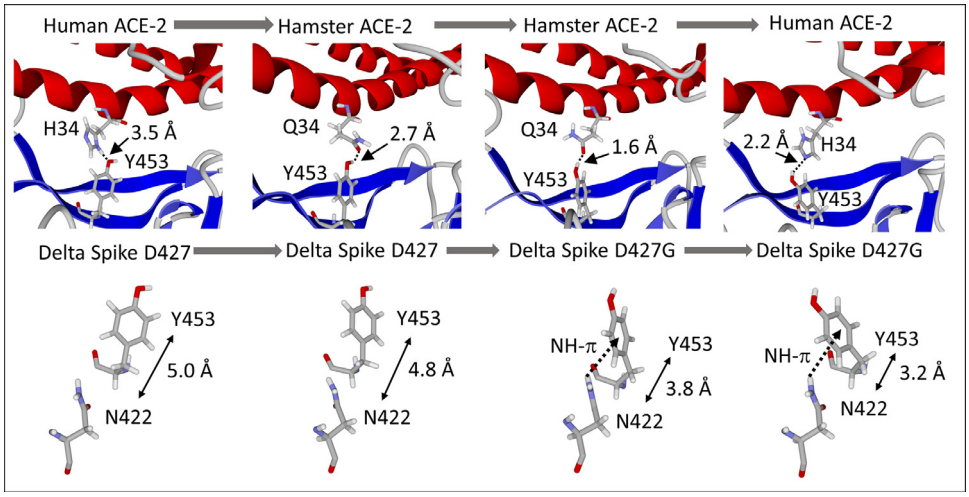

Fig. 1. Molecular modeling study of Delta spike (K417N/L452R/T498K) binding to human or hamster ACE2
Upper panel. Different scenarios of Interaction between Y453 and H34/Q34
From left to right: Delta variant spike protein bound to human ACE-2, same Delta spike protein bound to hamster ACE-2, Hamster-adapted Delta spike protein bearing the mutation D427G bound to hamster ACE2, same Hamster-adapted Delta spike protein with D427G bound to human ACE-2. The distance in indicate the length of the H-bond between the OH group of Y453 and a nitrogen atom from the imidazole ring of H34 or the NH2 of the amide group of Q34.
Lower panel. Distance between N422 and Y453 measured for each scenario
In absence of the D427G mutation, there is no direct interaction between the side chains of N422 (NH2 of the amide group) and the aromatic ring of Y453 (left panels). In presence of D427G, a long-range conformational change breaks the short α-helix displaying N422, resulting in a higher flexibility of the side chain of this amino acid so that it can form a NH-π bond with the aromatic ring of Y453. By attracting Y453, N422 gives more room to Q34 in hamster ACE-2. When the D427G hamster-adapted Delta variant infects humans back, this gain of flexibility optimizes the H-bond between Y453 and H34 (2.2 Å compared with 3.5 Å before the occurrence of D427G).

variant, in particular if it will display a higher virulence than the Delta variant or overcome the protection acquired with the vaccines. Nevertheless, it represents a potential threat and its human-to-human transmission should be carefully monitored.

Author contributions

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Institutional review board statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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