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Viewpoint

Defusing SARS-CoV-2: Emergency Brakes in a Vaccine Failure Scenario

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ABSTRACT: Deactivation of primed SARS-CoV-2 prior to cell entry constitutes an emergency brake in COVID-19 infection if vaccine-induced antibodies fail to block recognition of the human angiotensin-converting enzyme 2 (hACE2) receptor. The timing and locus for the therapeutic intervention are dictated by the cell entry mechanism and by the selective advantage of the dominant D614G mutation.

KEYWORDS: *SARS-CoV-2, COVID-19, evolutionary change, antibody, structural biology, virus transmissibility*

DEFUSING SARS-COV-2 AS IT GETS PRIMED FOR CELL ENTRY

There is a moment in the process of infection when SARS-CoV-2 offers a vulnerable flank, providing an opportunity that needs to be seized by targeted molecular intervention to effectively defuse the virus.[1−4] The virion structure opens up partially, and it does so for functional reasons at a particular juncture: During virus priming for cell entry, the assemblage of the spike (S) glycoprotein loosens up to enable the virus to penetrate the host cell membrane,[3] and at that point, the virus becomes vulnerable.[2] An assessment of the structural impact of a recent dominant mutation in the virus sheds light on a therapeutic strategy. The D614G substitution in the S glycoprotein becomes dominant[5] precisely because it entails a selective advantage resulting from holding together the spike when it penetrates the host cell to induce membrane fusion.[6] This selective advantage translates into higher infectivity of the G614 strain, as the anchoring of the host cell is properly coordinated with the cell-penetration step, a result squarely at odds with the standard interpretation of the experiments on cell entry that has the S glycoprotein quaternary structure dismantled for cell penetration, with domains S1 and S2 split apart.[7] Recent experimental evidence points to the contrary, as it identifies the culprit for higher penetration efficacy in the G614 strain.[6,8] Accordingly, in this study we argue that the culprit[6,8] for the rapid propagation of the D614G mutation[9] sheds light on the locus and timing for a targeted therapeutic intervention geared at deactivating the virus by disrupting its quaternary assemblage.

Recent evidence suggests that the opportunity for therapeutic intervention arises specifically at the preactivation stage for virion-mediated membrane fusion, when the quaternary structure of the S glycoprotein partially opens up to wield a functional role associated with the clipped S2 domain.[1−3] At that stage, the junction of domains S1 and S2 in the spike (S) protein is enzymatically cleaved, and S2 gets primed to penetrate the host cell by exposing its fusion peptide (FP).[3] Cell penetration can only occur if the host human cell is anchored nearby via S1/human angiotensin-converting enzyme 2 (hACE2) receptor binding (Figure 1a,b). That means that a noncovalent S1/S2 association, compensating for the cleavage of the S1/S2 junction, must be sufficiently stable to effectively bring the host cell membrane to the proximity of the FP, thereby initiating membrane fusion. While cleavage is of course essential to expose the FP in S2, an overlooked factor in the mechanism of virus transmission is the fact that the attachment of S1 to S2 is also essential to enable S2 to target the anchored host cell kept within reach via the S1/hACE2 binding. In this scenario, a structural analysis of the impact of recent evolutionary change in the virus[4] holds the key to the therapeutic intervention: The dominant mutation D614G in the S-protein stabilizes the S1/S2 association interface, significantly enhancing transmissibility;[4,6,8] therefore, therapeutic intervention must precisely disrupt the S1/S2 interface. In other words, the selective advantage of substitution D614G consists of reducing S1 shedding,[4,6,8] thus enhancing the cell-penetration efficacy of the spike. The therapeutic intervention must therefore reverse this effect, promoting S1 shedding, even beyond the levels found in strain D614, by disrupting the S1/S2 interface (Figure 1c).

The chances of disrupting the S1/S2 interface in the dominant G614 strain are high. This is because a highly immunogenic region has been identified that includes the structural defect in S1 created by the D614G substitution.[2] Thus, an antigen covering the packing defect[2] may be exploited within a suitable platform to generate or induce antibodies that target the S1 side of the S1/S2 interface precisely where the structural defect arises.

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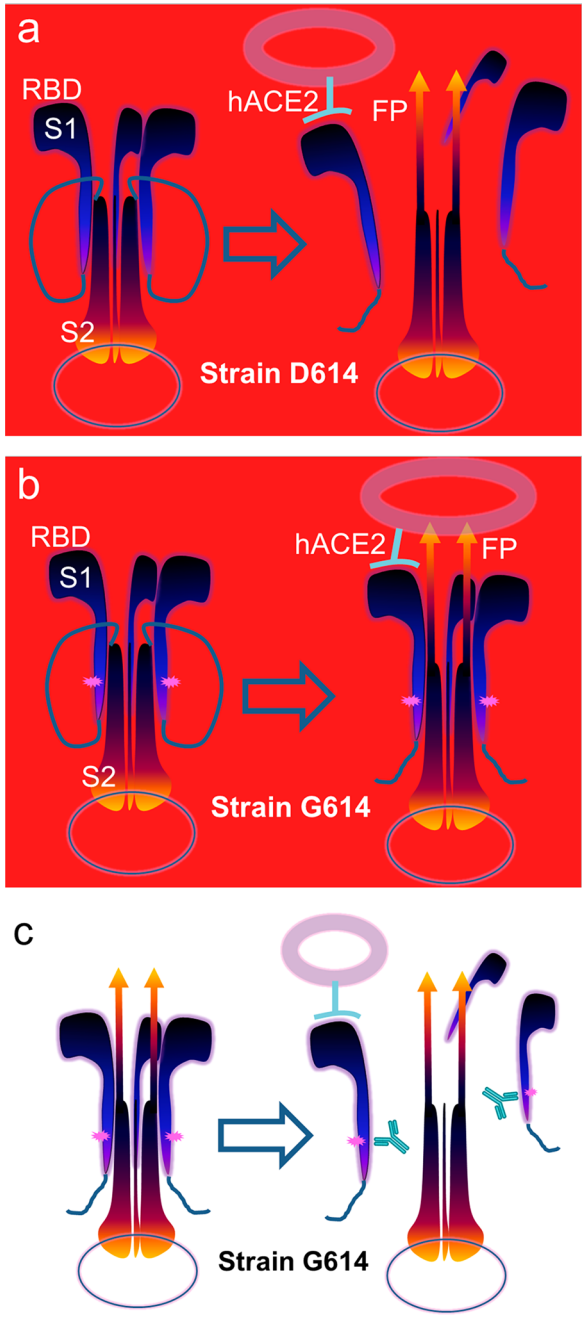

Figure 1. Scheme of the preactivation step for virion-mediated membrane fusion in strain D614 (a), strain G614 (b), and therapeutically intervened strain G614 of SARS-CoV-2 (c). (a) Due to S1 shedding in strain D614, the host cell sometimes fails to stay within reach for FP (arrow) penetration. (b) In dominant strain G614, due to the stabilization of the S1/S2 noncovalent interaction, the anchored host cell gets exposed to FP penetration. (c) The antibody-induced S1 shedding in strain G614 defuses viral transmission. The structural defect induced by the D614G substitution is highlighted by a detonation symbol. RBD stands for receptor-binding domain, and the host cell is represented by a light purple ellipse.

DISCUSSION

We have delineated an opportunistic route to defuse SARS-CoV-2 suggested by its recent evolutionary history and by the mechanism of cell entry. The therapeutic intervention aims at disrupting the spike assemblage during the activation phase for cell entry, so as to disconnect S1-mediated anchoring of the host cell from cell penetration by the primed S2 subunit. The clues for the discovery are found in the selective advantage of the D614G mutation that holds the spike together at cell entry by destabilizing the uncomplexed S1 subunit, hence favoring S1/S2 complexation. The direct deactivation of SARS-CoV-2 as it gets primed for cell entry may serve as an emergency brake in COVID-19 infection in case vaccine-induced antibodies, currently under accelerated development, fail to block the viral S1-mediated recognition of the hACE2 receptor.

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Notes

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