Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Immunology Letters 230 (2021) 63–64

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Correspondence

Are the emerging SARS-COV-2 mutations friend or foe?

After the explanations of UK Prime Minister that early analyses showed a new strain of SARS-CoV-2 could increase the reproductive rate by 0,4 or more and that it may up to 70 % more transmissible that the old variant, the Government impose harsher restrictions during the festive season. Furthermore, many countries have since imposed ban on travel to and from the UK. Now, there are fears that the new strain in the UK is spreading much faster.

Viruses change all the time. SARS-CoV-2 mutates regularly, acquiring about one new mutation in its genome every two weeks. Therefore, approximately 4,000 mutations have been identified in SARS-CoV-2. However, they all have been considered as redundant since they did not affect the behavior of the virus [[1]]. Coronaviruses have a large genome and encode a 3′-to-5′-exoribonuclease that permits high-fidelity replication and a range of tolerated variation by the viral RNA-dependent RNA polymerase [[2]]. This coronavirus exonuclease extends the coronavirus genome size through preventing lethal mutagenesis imposed by error rates of viral RNA polymerase [3]. Although, SARS-CoV-2 sequence diversity is reported to be very low [4], SARS-CoV-2 could acquire rare but favorable mutations with fitness advantages and immunological resistance due to natural selection [5].

Despite this uniquely high fidelity of replication, a number of mutations to the SARS-CoV-2 genome have been observed throughout the present course of the COVID-19 pandemic. Among SARS-related coronaviruses (Sarbecoviruses), only SARS-CoV-2 possesses a polybasic furin cleavage site at the S1-S2 junction in the Spike (S) protein, which is critical to human infection and transmission [6,7]. However, the furin cleavage site may have rendered the S protein less stable and therefore the virus may need mutation(s) to compensate for this instability. The acute selective pressure of S protein instability, which has been an Achilles' heel of the SARS-CoV-2, most probably was resolved by the highly emphasized D614 G mutation [7].

The trimeric spike protein mediates virus attachment and entry into host cells. Each monomer is comprised of an S1 subunit, which contains the receptor-binding domain (RBD), and an S2 subunit that mediates membrane fusion [8]. The spike protein is a string of 1273 amino-acids; in the original form from Wuhan (China), the 614th of these amino acids has aspartic acid (D), while in the mutated form, the 614th amino acid is glycine (G). This is a non-synonymous mutation, which is being carried along as a part of a clade called the "G clade" by GISAID that is named for this mutation [4]. D614 G mutation is emerged early during the pandemic, and viruses containing G614 are now dominant form of the virus globally [5].

The pattern of spread, combined with increased infectivity, suggests the mutation gave the virus a fitness advantage for transmission. This mutation is outside of the RBD in the S1 subunit of spike and has the potential to influence the conformation and flexibility of the spike protein. The D614 sidechain can form a hydrogen bond with the neighboring protomer T859 amino acid. Therefore, this interaction could be critical, because it could bridge residues from the S1 region of one protomer to the S2 region of an adjacent protomer, bringing furin and S2 cleavage sites closer. Furthermore, it potentially could attenuate shedding of S1 from the viral-membrane-associated SH2 [4,9]. Remarkably, it has also been reported that D614 G mutation may also reason in the stabilization of intermolecular interactions between S1 and S2, thus a decreased shedding of S1 [7].

The RBD of the SARS-CoV-2 spike undergoes hinge-like conformational movements, which transiently hide or expose the epitopes to engage a host cell receptor. These two states are referred to as the "down" conformation and the "up" conformation, respectively, where down corresponds to the receptor-inaccessible state and up corresponds to the receptor-accessible state. Importantly, the "up" or open conformation is thought to be less stable [9][10]. However, the open conformation is required for ACE2 binding because the ACE2 binding site is partially shielded in the closed conformation [11]. D614 G mutation attenuates the hydrogen-bond interaction with T859 from a neighboring protomer of the spike trimer, which allosterically promotes the RBD domain to an "up" conformation for receptor ACE2 binding and fusion, leading to an enhanced virion infectivity [8]. Altogether, mutational substitution of G614 can reduce the release of S1. Furthermore, the open conformation of variant RBD in the spike trimer can also lead to the exposure of epitopes that potentiate both the enhanced transmission and the vulnerability to host immune attack.

Patients infected with viruses containing G614 had higher levels of virus RNA, but there was no difference in hospitalization outcomes [5]. Furthermore, there seems to be an association between age and genotype, with younger patients more likely to carry 614 G viruses. Social contact surveys have demonstrated decreasing rates of contact after the age of 40, which is suggestive of lower transmission rates in older age groups. There is also no further indication that patients infected with the spike 614 G variant have higher COVID-19 mortality or clinical severity [12].

The RBD of the SARS-CoV-2 spike glycoprotein is a dominant target of neutralizing antibodies. Most SARS-CoV-2 vaccines were originally designed by using the ancestral D614 variant of the spike protein. An important question is whether any mutations that have appeared in circulating SARS-CoV-2 isolates have functional consequences. However, those above mentioned data suggest the D614 G substitution does not alter significantly SARS-CoV-2 morphology, spike cleavage pattern and neutralization properties. The D614 G mutation causes the virus to infect cells more efficiently but also creating a pathway to the virus' vulnerable core. With one flap open, it is easier for antibodies to infiltrate and disable the virus [10]. In conclusison, 614 G variant became modestly more susceptible to neutralization by host antibody responses as a consequence of acquiring a mutation that provides a fitness advantage for transmission [8,9]. Consistently, the SARS-CoV-2 spike protein with the G614 mutation cannot escape neutralization, but rather is candidate for neutralization at a higher level in humans who are immunized with vaccine [9]. Therefore, this critical finding may alleviate the

https://doi.org/10.1016/j.imlet.2020.12.014
Received 28 December 2020
Available online 2 January 2021

current concern for most vaccines being implemented around the world.

The novel UK variant, known as VUI-2020/01 or lineage B.1.1.7 carries 14 defining mutations in the spike protein [1]. This variant has a mutation in the RBD of the spike protein at position 501, where amino acid asparagine (N) has been replaced with tyrosine (Y). N501Y mutation, which is one the key six contact residues within the RBD, increases the binding affinity of virus to ACE2 receptor [13]. Another mutation at position 681, P681H, which is immediately adjacent to the furin cleavage site renders it more suitable for hydrolysis by TMPRSS2 and thus augmenting the viral fusion [14]. Since N501Y and P681H were previously observed independently, the UK variant is important as it contains both N501Y and P681H in combination. Remarkably, this new variant also carries a deletion mutation in another viral gene, ORF8, which was previously associated with a milder clinical infection and less post-infection inflammation [1,15].

Many mutations to the RBD are well tolerated with respect to both protein folding and ACE2 binding, which are two key factors for viral fitness. However, the ACE2 binding interface is more constrained than most of the RBD's surface, which could limit viral escape from antibodies that target this interface. N501Y variant shows a doubling of the occupancy of the open state with the concomitant decrease of the closed state [16]. Therefore, N501Y has a strong potential to contribute to increased transmission [17]. However, an increase in the open state of N501Y variant may also augment the antibody neutralization of the virus.

In the light of these data regarding the two important SARS-CoV-2 variants, the points to be emphasized can be listed as follows.

1 In the ancestral virus (SARS-CoV-2 D634 and N501), RBD is in down conformation, which means the receptor is in more stable and inaccessible state. Consequently, the old variant demonstrates higher resistance to the host immunity, comparing the new variants. In other words, while the ancestral SARS-CoV-2 is in the most stable and immune-resistant conformation, emerging mutations would limit the immune evasive features of the virus and cause it to become more easily controllable.
2 These new mutations clearly provide a fitness advantage for transmission. However, relatively better-concealed D614 receptor-binding domain of old variant is likely to be advantageous for immune evasion. Hence, there would be most probable fitness tradeoffs for D614 G and N501Y due to the more open conformation of its RBD, which potentially renders these new variants more immunogenic.
3 The deletion mutation of ORF8 in the most recent UK variant may cause a milder clinical infection and less post-infection inflammation as happened in Singapore [15].
4 The current evidence suggests that these mutations are less important for COVID-19 than other risk factors, such as age or comorbidities [5]. Therefore, if patients in the risk group can be better protected, while new SARS-CoV-2 mutations increase the transmission of infection, they become vulnerable to natural or vaccine-induced immunity that, in turn, may promote the faster development of herd immunity.
5 Finally, the bat virus RaTG13, which was identified as the closest known relative of SARS-CoV-2, has substantially lower affinity for ACE2 than SARS-CoV-2 because of the presence of affinity-decreasing mutation of N501D [6]. Hence, it would not be surprising to expect the possibility of the N501D variant instead of N501Y during future mutations and therefore the virus to self-inactivate.

In conclusion, although it is absolutely required to wait for the results of clinical and epidemiological data, we could hope for a better future instead of being pessimistic due to current mutations.

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Adnan Erol
Internal Medicine, Silivri, Istanbul, Turkey
E-mail address: eroladnan@protonmail.com.