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Original article

SARS-CoV-2 genetic diversity: Its impact on vaccine efficacy

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ABSTRACT

SARS CoV 2 S-glycoproteins play a crucial role in the entry steps of viral particles. Due to their surface location, they are the main target for host immune responses and the focus of most vaccine strategies. The D614G mutation identified in late January became dominant during March 2020, rendering SARS-CoV-2 more infectious. In April 2020, the Alpha, Beta and Gamma variants emerged simultaneously in Asia, South Africa, and South America, respectively. They were 1.6 to 2 times more transmissible than the ancestral strain.

The currently dominant Omicron variant (BA.2) is not a direct descendant from the D614G lineage, but rather emerged from the BA.1 variant (as did BA.4 and BA.5). It is substantially different from all the other variants. It presents significantly reduced susceptibility to antibody neutralization: after 2 doses of mRNA-vaccine, neutralizing titers to Omicron are 41 to 84 times lower than neutralization titers to D614G. That said, a booster dose of mRNA-vaccine increases Omicron neutralization titers and reduces the risk of severe infection.

1. Introduction

Like other coronaviruses, SARS-CoV-2 has a crown-like appearance explained by the low density of spike (S) glycoproteins protruding from the surface of mature virions. S glycoproteins play a crucial role in the viral particles' entry steps. Due to their surface location, they are the main target for host immune responses and the focus of most vaccine strategies. The spike (S) glycoprotein is a trimeric protein made up of three proteins in "open" or "closed" conformations. The more they are open, the easier it is for the glycoprotein to bind to the cellular surface receptor angiotensin-converting enzyme 2 (ACE2) through the receptor-binding domain (RBD) and for SARS-CoV-2 to infect host cells [1].

The D614G mutation was spotted in late January 2020 in western Europe and became dominant during March 2020, rendering SARS-CoV-2 more infectious. By relaxing connections between the three proteins of the spike (S) glycoprotein, the D614G mutation makes open conformations more likely and increases the likelihood of infection [1]. Although this mutation does not directly occur on the receptor-binding domain, it increases viral fitness before the emergence of variants. All current viruses descend from the genogroup carrying the D614G mutation.

In April 2020, the Alpha, Beta and Gamma variants emerged simultaneously in Asia, South Africa, and South America, respectively. They were 1.6 to 2 times more transmissible than the ancestral strain [2]. All of them carried mutations on crucial positions in the RBD (N501, E484, T478) or close to the RBD (K417) showing convergent evolution. These mutations, especially N501, enabled the Alpha variant to gradually replace the ancestral D614G strain. The Beta and Gamma variants failed to sufficiently compete on a planetary scale. The Alpha variant was then replaced by the Delta variant, with increased fitness (Table 1).

Even though the Alpha, Beta, and Gamma variants carried affinity-enhancing mutations in the RBD, the effects of these mutations could differ according to their arrangements. The phenomenon through which the expression of one gene is affected by the expression of one or more independently inherited genes is called epistasis. Epistatic relationships among RBD mutations can substantially chfange the RBD's binding affinity and increase the risk of immune escape [3]. For example, K417 alone is an affinity-decreasing mutation that can become an affinity-enhancing mutation combined with the N501 and E484 mutations.

Most evidence suggests that the spread of these viruses was explained by mutations affecting the affinity of the RBD to its target (ACE2 receptor) and not by escape from antibodies.

Mutations and conformation changes in the spike (S) glycoprotein can also cause immune evasion. The most effective immune response involves RBD-targeted neutralizing antibodies, of which the capacity to bind to the RBD can be altered by key mutations in this area. The antibody landscape is currently used to assess the anti-spike antibody response of each strain. Antibody landscape is a method for quantitative analysis of antibody-mediated immunity to antigenically variable pathogens, achieved by

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Table 1
Timeline of the emergence of COVID-19 variants.

Timeline	Geography	Mutations					Variant of Concern	Pango lineage	Theoretical R0	Immune escape	Impact on severity
		D614G	N501Y	E484K	T478K	K417N					
December 2019	**Wuhan**										
February 2020	Europe	+							3		
September 2020	UK	+	+				**Alpha**	**B.1.1.7**	x 1,6 to 2	Increased	Increased
October 2020	South Africa	+	+	+		+	**Beta**	**B1.351**			
December 2020	South America	+	+	+		+	**Gamma**	**P.1**			
October 2020	India	+		+	+		**Delta**	**B.1.617.2**	x 2,6	Increased	Increased
November 2021	South Africa						**Omicron**	**B.1.1.529**	Unclear	Increased	Reduced

accounting for antigenic variation among pathogen strains [4]. It has been used for influenza virus infections and as a means of evaluating vaccine composition. By assessing antibody-mediated protection, this method showed that vaccination with an ancestral strain enabled protection against all the variants to be obtained.

The currently dominant Omicron variant (BA.2) is not a direct descendant from the D614G lineage, but rather emerged from the BA.1 variant (as did BA.4 and BA.5). This virus carries at least 35 mutations on the spike (S) glycoprotein, especially key mutations on the receptor-binding domain (RBD). Some of them were previously known enhancing-affinity mutations and some of them are new. These modifications of RBDs and spike (S) glycoproteins are responsible for greater transmissibility and immune escape than the Delta, and allowed the Omicron variant to become dominant in just two months. Several Omicron mutations affect the structure of the spike (S) glycoprotein, particularly in a lipid-binding pocket, which is occupied by linoleic acid in an unusually rigid state, and all RBDs are found in a locked-down configuration. Mutations in this area tend to empty this pocket and the loss of lipid promotes RBD presentation to the target cell [5].

Antigenic landscape has shown that Omicron substantially differs from all other variants. It presents significantly reduced susceptibility to antibody neutralization. Neutralizing titers against the Omicron variant are 41 to 84 times lower than neutralization titers to D614G after 2 doses of mRNA-vaccine. A booster dose of mRNA-vaccine increases Omicron neutralization titers and may substantially reduce the risks of symptomatic breakthrough infections [6].

Viral evolution was first focused on the receptor-ligand interaction (mutation on the RBD and conformation of the spike protein) and we are now observing more immune escape phenomena, especially with Omicron. Many questions remain: What will be the evolution of the BA.2 sublineage, which has increased transmission potential compared to BA.1? Is vaccine composition modification necessary, given the data from the antibody landscape showing insufficient protection with a two-dose regimen, or will booster doses suffice?

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Authors' contributions

All authors contributed equally to this work.

Declaration of interest

The authors declare no conflict of interest

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