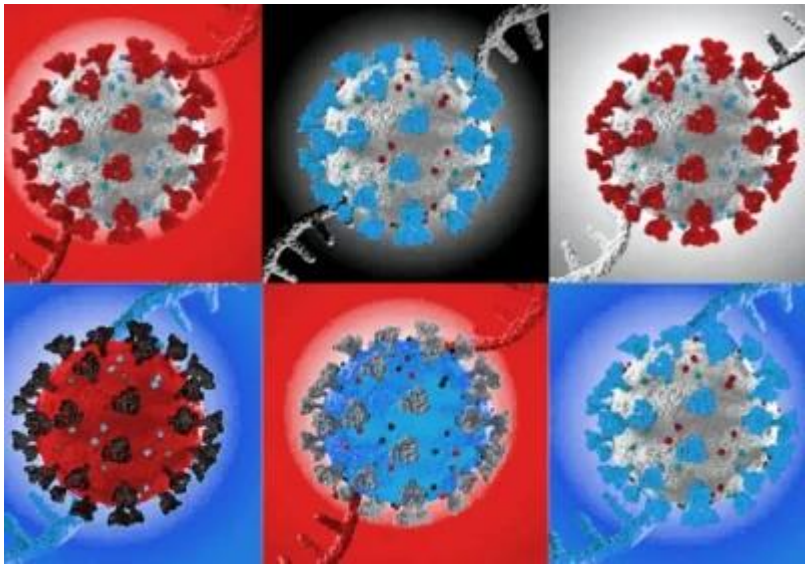
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded RNA virus. With its continuous evolution, numerous variants have emerged. These variants, which are classified as variants of concern (VOCs) or variants of interest (VOIs) by the World Health Organization, carry an unprecedented number of mutations in the receptor-binding domain (RBD) of the S protein. They can evade the herd immunity induced by natural infection, leading to the loss or reduced efficacy of most previously approved vaccines and monoclonal antibodies. A recent study by Chinese researchers proposes the classification of SARS-CoV-2 variants into five serotypes based on the antigenicity of the receptor-binding domain (RBD).

SARS-CoV-2's genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein. The S protein is a glycosylated homotrimer with each monomer composed of subunits S1 and S2, separated by host cell proteases. The S1 domain comprises the N-terminal domain (NTD), the RBD with a receptor binding motif (RBM), and two C-terminal domains. The RBD in the S1 subunit plays a crucial role in determining the efficiency of viral entry into host cells, as it directly interacts with the human angiotensin-converting enzyme 2 (ACE2) receptor. The SARS-CoV-2 variants with more RBD mutations tend to be more immune-evasive, while still highly transmissible.

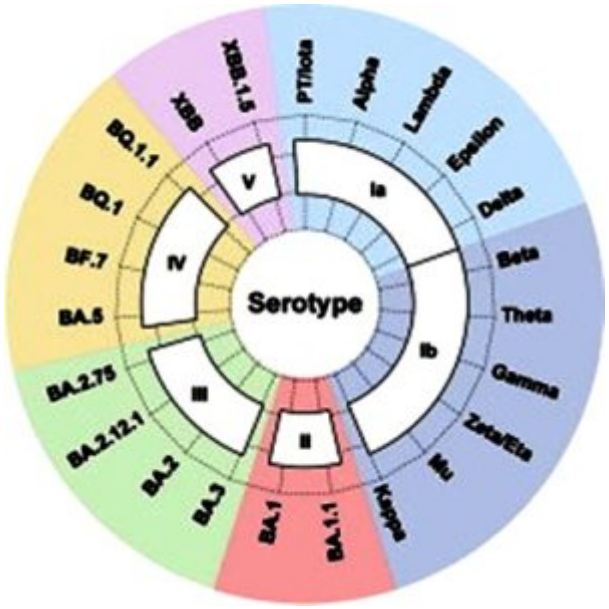
The authors emphasized that the classification of viral serotypes has proven to be pivotal in preventing and controlling viruses. They stated that Dengue virus, for example, is classified into four serotypes, each encompassing multiple diverse genotypes. The immunogenicity of vaccine candidates for Dengue virus has always been evaluated based on their ability to neutralize four serotypes. The establishment of distinct serotypes can provide a foundation for a rapid evaluation of newly emerged variants.



About the study

This classification of serotypes was based on the assessment of cross-neutralization of antisera using RBD-based mRNA vaccines to simulate infection with different SARS-CoV-2 variants. The researchers conducted a systematic characterization of the antigenicity of 23 representative SARS-CoV-2 variants, including the prototype (PT), pre-Omicron VOCs, pre-Omicron VOIs, and Omicron sub-variants BA.1, BA.2, BA.5, XBB, and their derivatives.

Based on a systematic assessment of the antigenicity of their RBD in the S protein, the 23 variants are classified into five distinct serotypes designated as serotypes, I, II, III, IV, and V. Each serotype contains several genetically distinct SARS-CoV-2 variants.



The illustration from the original article by Hu S, Wu C, Wu X et al. Science Bulletin. 2023

All pre-Omicron variants were classified as serotype-I (with two subtypes) since they all potently cross-react with each other. Two subtypes, serotype-Ia (PT, Alpha, Lambda, Epsilon, or Lambda) and serotype-Ib (Beta, Theta, Gamma, Zeta, Mu, and Kappa) were classified within serotype-I. All serotype-Ib variants had the E484K/Q mutation in RBD, while all serotype-Ia variants (PT, Alpha, Lambda, Epsilon, and Delta) did not. According to the authors, these results suggest that the additional immunogenicity of serotype-Ib may be attributed to the presence of the E484K/Q mutation.

The remaining four serotypes all comprise Omicron sub-variants at various stages of evolution. The BA.1 and BA.1.1 subvariants were classified as serotype-II because they only cross-react with BA.1 and BA.1.1, which was unique among all selected variants. Based on the similarity of their neutralization spectra, the remaining Omicron subvariants were classified into three serotypes, with BA.3, BA.2, BA.12.1, and BA.2.75 being serotype-III, BA.5, BF.7, BQ.1, and BQ.1.1 being serotype-IV, and XBB, XBB.1.5 being serotype-V.

Importantly, the Omicron sub-variants showed a consecutive antigenic shift, with variants in serotype-III evading variants in serotype-II, which in turn were evaded by serotype-IV variants, and further evaded by serotype-V variants. Each Omicron subvariant exhibited specific cross-reaction with the variants in the preceding serotype. This indicates that evading the previously dominant variant was the primary driving force behind the evolution

of the Omicron subvariants.

Importantly, no such consecutive antigenic shift was observed during the transition from serotype-I to serotype-II, suggesting that Omicron was not a direct decedent of the prevalent variants immediately before its emergence. This observation is consistent with previous analyses of two Japanese scientists who concluded that the formation of part of the Omicron isolates BA.1, BA.1.1, and BA.2 was not the result of genome evolution, such as the accumulation of mutations and homologous recombination, as is common in nature. They emphasized that the SARS-CoV-2 isolates are formed by a completely new mechanism that cannot be explained by previous biology. It is highly unlikely that these viruses arose spontaneously.
https://discovermednews.com/omicron-variants-may-have-been-artificially-synthesized-rather-than-naturally-formed/

Conclusion

This study proposes the classification of SARS-CoV-2 variants into five serotypes based on the antigenicity of the RBD, with all pre-Omicron variants classified as serotype-I, and Omicron sub-variants classified as serotype-II, III, IV, and V according to their stages of evolution. The authors emphasized that the antigenicity of SARS-CoV-2 could be influenced by proteins other than the S protein, or by domains of the S protein other than RBD, although RBD is the most antigenic domain in SARS-CoV-2. They suggested that this classification could facilitate the rapid determination of the serotype of newly emerged SARS-CoV-2 variants.

This article was published in Science Bulletin.

Journal Reference

Hu S, Wu C, Wu X et al. Classification of five SARS-CoV-2 serotypes based on RBD antigenicities. Science Bulletin. In press. (Open Access).
https://doi.org/10.1016/j.scib.2023.09.048