Omicron: a shift in the biology of SARS-CoV-2

The Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a phenotype that has changed fundamentally compared with preceding variants. Substantial antigenic change within the spike protein and a new endocytic entry mechanism underlie the immune evasion characteristics and a coincident decrease in the virulence of this variant.

This is a summary of:
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The problem

When scientists in South Africa first identified the Omicron variant of SARS-CoV-2, there was real concern for the potential of a new global wave of infection. Such apprehension stemmed from the predicted structure of the spike protein, indicating that the virus had changed substantially, thus presenting a potential risk of vaccine escape (Fig. 1)[1]. The emergence of the virus in the United Kingdom was monitored by the UK public health agencies and members of the COVID-19 Genomics UK (COG-UK) Consortium by high-throughput sequencing. As predicted, Omicron rapidly outpaced the preceding Delta variant, although, fortuitously, early signals suggested that it was associated with less severe disease. In this study, we explored the immune evasion characteristics of the Omicron variant through assays of immune function and through estimates of real-world vaccine effectiveness. We further investigated the biological properties of the virus in vitro, in order to understand the mechanisms of reduced disease severity.

The discovery

Neutralizing antibodies and spike-specific T cells were quantified in samples from recipients of deployed vaccines in the COVID-19 Deployed Vaccine Cohort Study (DOVE). Vaccine effectiveness was estimated in the Evaluation of Variants Affecting Deployed COVID-19 Vaccine (EVADE) study that links vaccine response with genetic variants in Scotland.

As suggested by the 'early warning' signal from sequencing data that predicted substantial immune escape[1], we found markedly reduced neutralization of Omicron BA.1 and BA.2 variants by sera from recipients of two or three doses of vaccine, while T cell responses were relatively preserved. These data were mirrored by a substantial reduction in real-world vaccine effectiveness, which was partially restored by booster vaccination. Attempting to understand the underlying cause(s) of immune escape, we studied the virological properties of Omicron in vitro and unexpectedly found that the variant did not induce cell–cell fusion, a phenomenon observed in preceding variants that results from activation of the spike protein at the cell membrane by the cell surface protease TMPRSS2. Instead, Omicron variants entered cells preferentially via a TMPRSS2-independent endosomal entry pathway, thereby altering the cell tropism of the virus. Experiments using chimeric spike proteins revealed that impaired cell–cell fusion was determined by changes within the receptor-binding domain (RBD) of the spike protein, while endosomal entry was associated with changes in the S2 domain. Such major changes in the antigenicity and replicative biology of the virus likely underlie the global spread and decreased virulence of Omicron.

Future directions

The immune evasion characteristics of Omicron were correctly predicted through genetic sequencing. It is possible, by building on high-scale genomic data, that future vaccines will incorporate multivalent designs that incorporate genetic variation of circulating variants or that may aim to stimulate responses that target more conserved epitopes.

The fundamental change in the viral entry mechanism was not predicted by sequencing data; rather it was revealed by observations of reduced syncytia formation in cell culture experiments from several laboratories[2,3] including our own, highlighting the necessity of in vitro studies to understand the mechanisms underlying changes in cell tropism and clinical severity of disease. Experiments using chimeric spike proteins may be particularly useful for predicting the likely cellular entry mechanisms and the susceptibility to neutralizing antibodies of novel recombinant variants as they arise.

Future work will be needed to characterize the key mutations within the RBD and S2 regions of the spike protein and their roles in determining cell fusion and cell entry. Such studies will provide a valuable insight into the expected virulence of future variants as they emerge over time, given that the ongoing evolution of SARS-CoV-2 is likely to bring future challenges and a trajectory of decreasing virulence cannot be guaranteed[4].

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EXPERT OPINION

"This is a significant and important study for understanding the impact on viral entry and immune evasion that makes Omicron the most significant variant of concern (VoC) to date. The study distils the effect of Omicron spike mutations for domain specific functions for antibody evasion, reduced cell–cell fusion, endosomal entry and proteolytic processing, providing a key resource for viral functions and an Achilles heel for targeted therapies. Commendations to the authors." **Sophie Valkenburg, The University of Melbourne, Melbourne, Victoria, Australia.**

FIGURE

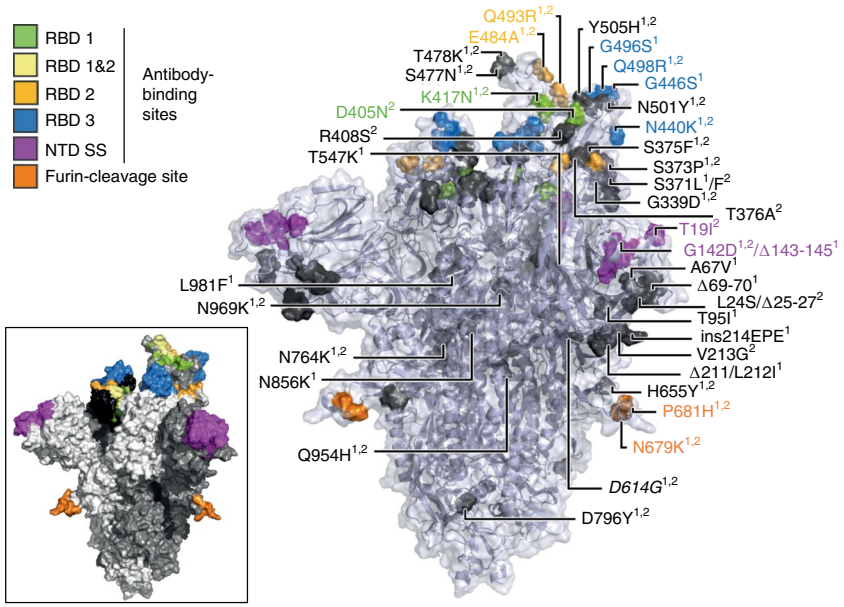

Fig. 1 | The Omicron spike protein. The spike homotrimer in open conformation with locations of Omicron substitutions, deletions (Δ) or insertions (ins) present in lineages BA.1 and BA.2. Mutated residues are highlighted as spheres with opaque surface representation. Residues impacting RBD-specific antibodies of classes 1, 2 or 3, or belonging to the N-terminal domain (NTD) antibody supersite, or comprising the furin-cleavage site are coloured. Inset shows these sites with remaining areas of the protein shaded to show the three monomers.

BEHIND THE PAPER

The emergence of the Omicron variant with a heavily mutated spike protein was of significant concern to the scientific community. We aimed to assess whether immunity conferred by existing vaccines would extend to Omicron. Pseudotype-based systems developed before the pandemic enabled rapid assessment of immune escape in vitro using sera from an observational study of recipients of deployed vaccines (DOVE). Assessing real-world vaccine effectiveness in Scotland required the establishment of a multidisciplinary team. The EVADE study brought together mathematicians, clinicians, data scientists, virologists and immunologists, enabling us to generate robust estimates of vaccine effectiveness. Early reports of reduced virulence suggested a fundamental alteration in viral biology. During the in vitro passage of the first clinical isolates of Omicron, we noted that the plaque size was curiously small, leading to subsequent investigations of syncytium formation, and the mechanisms of viral entry. **B.J.W. and E.C.T.**

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FROM THE EDITOR

"The Omicron variant evades vaccine-induced neutralization capacity, fails to form syncytia, shows reduced replication in human lung cells and uses a different cell entry pathway. Here the authors discover that altered fusion and cell entry characteristics are linked to distinct regions of the Omicron spike, which could explain why replication in the upper airway is enhanced in this variant." **Danielle Troppens, Associate Editor, *Nature Microbiology*.**