The puzzling mutational landscape of the SARS-2-variant Omicron

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Abstract
The recently emerging SARS-CoV-2 variant omicron displays an unusual association of 30 mutations, 3 deletions, and 1 insertion. To analyze the impact of this atypic mutational landscape, we constructed a complete structure of the omicron spike protein. Compared with the delta variant, the receptor-binding domain (RBD) of omicron has an increased electrostatic surface potential, but a decreased affinity for the ACE-2 receptor. The N-terminal domain (NTD) has both a decreased surface potential and a lower affinity for lipid rafts. The omicron variant is predicted to be less fusogenic and thus less pathogenic than delta, due to a geometric reorganization of the S1-S2 cleavage site. Overall, these virological parameters suggest that omicron does not have a significant infectivity advantage over the delta variant. However, in omicron, neutralizing epitopes are greatly affected, suggesting that current vaccines will probably confer little protection against this variant. In conclusion, the puzzling mutational pattern of the omicron variant combines contradictory properties which may either decrease (virological properties) or increase (immunological escape/facilitation) the transmission of this variant in the human population. This Janus-like phenotype may explain some conflicting reports on the initial assessment of omicron and provide new insights about the molecular mechanisms controlling its dissemination and pathogenesis worldwide.

KEYWORDS
antibody susceptibility, coronavirus, evolution, infection, pathogenesis, SARS coronavirus, virulence, virus classification

1 | INTRODUCTION

Omicron (B.1.1.529) is a SARS-CoV-2 variant that recently emerged in southern Africa and in several European countries.1 It was first detected in South Africa at the beginning of November 2021 and as of 16/12/2021, 7277 genomes were available from the GISAID database (https://www.gisaid.org/), mostly from South Africa (n = 1130) and from the United Kingdom (n = 4116). Although in most regions the prevalence of omicron is currently low compared to delta that accounts for 1387376 genomes since 01/11/2021, this variant surprised many people as it carries an unusual number of mutations in its spike protein: 30 mutations, 3 deletions, and 1 insertion (Table 1). For comparison, the delta variant B.1.617.2 has only 9 mutations and 1 deletion. Omicron was designated a variant of concern (VOC) on 26/11/2021.2

So far, the analysis of omicron has given a series of various and somewhat paradoxical results. First, its mutational pattern does not seem to result from the direct evolution of a known variant, and in particular, it does not derive from the delta variant, which has been dominant worldwide during the last months of 2021.3 Indeed, the omicron variant lacks the typical L452R mutation which is characteristic of most delta variants.6,7 Second, initial assessments of omicron propagation in South Africa and some European countries (Denmark, UK, and France) indicated
T A B L E 1 Mutational pattern and T-index of SARS-CoV-2 variants delta and omicron

| Variant       | Mutations—NTD                                      | Mutations—RBD                                      | Mutations—rod                                      | T-index | I-index |
|---------------|----------------------------------------------------|----------------------------------------------------|----------------------------------------------------|---------|---------|
| Delta B.1.617.2 | T19R T95I G142D \(\Delta E156 \Delta F157 R158G\) | L452R T478K                                       | D614G P681R D950N                                 | 10.81   | 3.10    |
| Omicron B.1.529 | A67V \(\Delta H69 \Delta V70\) T95I G142D \(\Delta V143 \Delta Y144 \Delta Y145 \Delta N211 L212I +214EPE\) | G339D S371L S373P S375F K417N N440K G446S S477N T478K E484A Q493R G496S Q498R N501Y Y505H T547K | D614G H655Y N679K P681H N764K D796Y N856K N954K N969K L981F | 3.90    | 5.80    |

Note: Transmissibility index (T-index) is calculated as follows (details previously published in ref.3 for alpha, beta, gamma, and delta variants):

\[
T \text{-index} = \frac{\Delta G_{\text{mut}}}{\Delta G_{\text{wt}}} \times \frac{\Delta G_{\text{mut}}}{\Delta G_{\text{nAb}}} \times \Delta G_{\text{ntAb}} \times \Delta G_{\text{ntAb}} \times \Delta G_{\text{ntAb}}
\]

For omicron: T-index = 0.83 × 0.77 × 1.24 × 4.93 = 3.90

The immune-escape index (I-index) is calculated as described in ref.4

\[
I \text{-index} = \frac{1}{2} \left( \frac{\Delta G_{\text{mut}}}{\Delta G_{\text{mut}}} \right) \times \frac{\Delta G_{\text{nAb}}}{\Delta G_{\text{nAb}}} \times \Delta G_{\text{ntAb}} \times \Delta G_{\text{ntAb}}
\]

The I-index of the original 20B strain is equal to 1.

Abbreviations: NTD, N-terminal domain; RBD, receptor-binding domain.

that this variant is highly contagious. However, this high transmissibility did not seem to correlate with a clearcut higher affinity of the omicron spike protein for the ACE-2 receptor: some groups reported a moderate increase of the receptor-binding domain (RBD) affinity for ACE-2, whether, in contrast, others reported a decreased affinity. To further complexify the problem, a third group concluded that delta and omicron spike proteins display a similar for ACE-2, due to compensation of mutations that either increase or decrease ACE-2 binding in the case of omicron. Third, in vitro experiments performed with culture cells also gave mixed results. In some cells, the infectivity and replication of the omicron variant were higher than delta, whereas in other cells opposite results were obtained, with delta being clearly more performant than omicron. Moreover, several reports suggest that the omicron variant spike confers impaired cell–cell fusion activity, which may correlate with low pathogenicity.

In face of such conflicting results, the aim of the present study was to provide a global in silico analysis of the omicron spike protein. To this end, we used a series of molecular modeling approaches to assess the affinity of the RBD for ACE-2, but also the avidity of the N-terminal domain (NTD) for lipid raft gangliosides. We also studied the electrostatic surface potential of both the RBD and the NTD, a critical parameter that controls the kinetic of interaction of the virus with the host cell membrane. Finally, we analyzed the impact of the delta and omicron mutational profiles on the affinity of neutralizing antibodies directed against the RBD and NTD of each variant.

2 | METHODS

2.1 | Mutational profile extraction

The mutational pattern of SRAS-CoV-2 variants was extracted as an excel file from the Los Alamos database (https://cov.lanl.gov/components/sequence/COV/int_sites_tbls.comp).

2.2 | Structural model of the omicron spike protein

A complete structure of the spike protein was generated from the original 20B strain (Wuhan + D614G, pdb 7bnm). All gaps in the pdb file were fixed by inserting the missing amino acids with Robetta [https://robetta.bakerlab.org/], a protein structure prediction service. The structure was then submitted to several rounds of energy minimization with the Polak-Robièvre algorithm as described previously. This source file model was used to introduce the specific mutational profiles of delta and omicron with the MUTATE tool of Swiss-PdbViewer.

2.3 | Electrostatic surface potential

The electrostatic potential was measured by the Molegro Molecular viewer (http://molexus.io/molegro-molecular-viewer). It is expressed as the sum of the Coulomb potentials for each atom of the protein, with a distance-dependent dielectric constant. Color intensities (negative in red, positive in blue, neutral in white) were quantified with the ImageJ software as described previously. Values >1 are indicative of an electropositive surface.

2.4 | Affinity of the spike protein for ACE-2

The ACE-2 RBD complex used as reference was obtained from pdb 6M0J (B.1 Wuhan strain). This model was optimized by energy minimization, raising the energy of interaction from \(\Delta G = -229\) kJ·mol\(^{-1}\) to \(\Delta G = -343\) kJ·mol\(^{-1}\). The affinity of delta and omicron RBDs for ACE-2 was estimated in comparison with this value after introducing the appropriate mutations in the optimized pdb file 6M0J.
2.5  |  Avidity of the spike protein for lipid rafts

The structural model of the NTD bound to lipid raft gangliosides (energy of interaction $\Delta G = -397$ kJ·mol$^{-1}$) was obtained and corrected for gaps as previously described.$^3$ The avidity of delta and omicron NTDs for lipid raft gangliosides was estimated in comparison with this value after introducing the appropriate mutations in the optimized reference model.

2.6  |  T-index analysis

The transmissibility index (T-index) of a SARS-CoV-2 variant combines kinetic and affinity parameters which govern virus binding to host cells. It gives an estimation of the overall interaction of the NTD with lipid raft gangliosides ($\Delta G_{\text{mut/nd}}/\Delta G_{\text{wt}}$ [NTD-ganglioside]), the affinity of the RBD for the ACE-2 receptor ($\Delta G_{\text{mut/nt}}/\Delta G_{\text{wt}}$ [RBD-ACE-2]), and the electrostatic surface potential of the NTD and RBD surfaces facing the host cell membrane.$^3$ It is calculated with the following formula:

$$\Delta G_{\text{mut/nt}}/\Delta G_{\text{wt}} = \Delta G_{\text{mut/nd}}/\Delta G_{\text{wt}} [\text{NTD-ganglioside}] \times \Delta G_{\text{mut/nt}}/\Delta G_{\text{wt}} [\text{RBD-ACE-2}] \times \left[ \text{Surface Potential}_{\text{NTD}} \times \left[ \text{Surface Potential}_{\text{RBD}} \right] \right].$$

2.7  |  I-index analysis

The immuno-escape index (I-index) evaluates the level of resistance of a SARS-CoV-2 variant to neutralizing antibodies (nAb) directed against the RBD and the NTD of the Spike protein.$^3$ It is calculated according to the following formula:

$$1/2 \left( \Delta G_{\text{mut/nt}}/\Delta G_{\text{wt}} [\text{RBD-nAb}] + \Delta G_{\text{mut/nt}}/\Delta G_{\text{wt}} [\text{NTD-nAb}] \right).$$

2.8  |  Scanning electron microscopy

The scanning electron microscopy image was obtained from a SARS-CoV-2 omicron-RNA-positive VeroE6 cell culture supernatant,$^{21}$ using a SU5000 microscope (Hitachi High-Technologies Corporation).

3  |  RESULTS

3.1  |  Structural analysis of the spike protein of delta and omicron variants

A structural model of the omicron spike protein was generated and compared to the one of the delta variant. In the case of omicron, mutations heavily affected the NTD, the RBD, as well as other critical regions including the proteolytic cleavage site and the fusion machinery (Figure 1A,8). The geometric reorganization of the protein around the S1-S2 proteolytic cleavage site of omicron (Figure 1A), due to the H655Y/N679K/P681H triad (vs. the single mutation P681R for delta), suggests that host cell surface proteases such as transmembrane serine protease 2 (TRMPSS2)$^{22}$ may not be equally active on both variants.

3.2  |  T-index analysis

To learn more about the infectivity and pathogenicity of the omicron variant, we applied to this variant the analysis of the T-index (transmissibility index) which had allowed us, soon after the appearance of the delta variant in April 2021, to anticipate its expansion globally.$^{2}$ This index takes into account the interaction of the NTD domain with the lipid rafts of host cell membranes,$^{3,16}$ the interaction of the RBD domain with the ACE-2 receptor,$^{23}$ and the electrostatic surface potential of both NTD and RBD which reveals the kinetics of virus binding to target cells.$^3$ Taken together, these critical parameters control the very first steps of SARS-CoV-2 infection, from the initial attraction of the viral particle by the cell surface, to ACE-2 binding.$^{3,16}$ Therefore, the T-index adequately reflects the relative infectivity of a SARS-CoV-2 variant compared to any other strain.

In the case of the omicron variant, some of these parameters were increased, but others were decreased when compared with the original 20B strain and to the delta variant. Indeed, the avidity of omicron spike NTD for lipid rafts was decreased by 17% ($\Delta G = -329$ kJ·mol$^{-1}$ for omicron vs. $-397$ kJ·mol$^{-1}$ for the reference NTD). The affinity of the RBD for ACE-2 was decreased by 23% ($\Delta G = -264$ kJ·mol$^{-1}$ for omicron vs. $-343$ kJ·mol$^{-1}$ for the reference RBD). The electrostatic surface potential of the NTD was decreased by 25% whereas it was increased by 3.8-fold for the RBD (Figure 1C, D). Based on these parameters, the T-index of the omicron variant was estimated to be 3.90 (Table 1). This value is high compared to the Wuhan/D614G strain (2.16),$^3$ but rather low compared to delta variants (10.67 for a variant with E484Q$^3$ and 10.81 for the B.1.617.2 variant studied here). In fact, the T-index of the omicron variant is in the same range as that of all other SARS-CoV-2 variants tested so far which, with the noticeable exception of the delta variant (T-index >10), have a T-index value <4.$^3$ (Figure 2).

A detailed analysis of the omicron spike protein reveals that its pattern of mutations does not obey a clearcut logic. For instance, the omicron RBD surface which faces ACE-2 is almost uniformly positive (Figure 1C), which does not fit optimally with the surface of ACE-2 which, although chiefly electronegative, displays several positive spots that will not allow a perfect adjustment with the RBD.$^3$ This is in line with the lower affinity of the omicron RBD for ACE-2 (Table 1). Similarly, the surface of the omicron NTD is not positive enough (Figure 1C) to perfectly interact with the electronegative lipid raft surface.$^3$ Indeed, the global analysis of the electrostatic surface potential of the trimeric spike protein revealed that the central area formed by the three RBDs is highly positive (potential value 4.93), whereas the lateral NTDs, which are far less electropositive (potential value 1.24), displayed a mosaic pattern combining a series of positive, negative and neutral spots (Figure 1D). Thus, the trimeric spike of the omicron variant does not follow the usual concomitant evolution of the NTD and RBD towards higher electropositivity.$^3$
3.3 | I-index analysis

Taken together, these data suggest that the omicron variant does not have a clearcut transmissibility advantage over the delta variant. However, other parameters may counterbalance these virological properties. In particular, the immune status of the host might be critical. The mutational pattern of the omicron variant greatly affects the spike surface that faces the host cell (Figure 1A,B). Correspondingly, the structural analysis of the omicron spike protein revealed that the main neutralizing epitopes are greatly affected by omicron mutations (Table 1). Indeed, the immuno-escape index (I-index) of omicron is 1.9-fold higher than the one of delta (5.8 vs. 3.1, respectively, given that the I-index of the Wuhan strain is 1.0). All other variants have an I-index <3, showing that as far as immune escape is concerned, this variant is far ahead of all competitors (Figure 2). Hence current vaccines will probably confer little protection against the omicron variant.

3.4 | Detection of the omicron variant in viral cultures

In Marseille, we have already deposited 18 genomes in GISAID as of 16/12/2021 (out of 62 for France). The picture (Figure 3) shows a SARS-CoV-2 omicron variant isolate from a supernatant of culture on VeroE6 cells. As a matter of fact, this picture is that of the first isolate of an omicron variant obtained from a patient in France. The present structural analysis was conducted promptly, and its results and interpretation were
available opportunely when the first cases of the omicron variant were detected in our geographical area and in France. It is therefore part of a necessarily polyphasic approach that allows the broadest characterization of a new variant.

4 | DISCUSSION

The main outcome of the present study is that the omicron variant has an atypical mutational pattern combining contradictory properties that may either decrease (intrinsic virological properties) or increase (immunological escape) the transmission of this variant in the human population. To the best of our knowledge, our analysis is the first one that considers all four escape) the transmission of this variant in the human population. To the best of our knowledge, our analysis is the first one that considers all four

available opportunely when the first cases of the omicron variant were detected in our geographical area and in France. It is therefore part of a necessarily polyphasic approach that allows the broadest characterization of a new variant.

FIGURE 3 Scanning electron microscopy of a SARS-CoV-2 Omicron-RNA-positive culture supernatant. Image was obtained using a SU5000 scanning electron microscope (SEM) (Hitachi High-Technologies Corporation). A viral particle is indicated by a white arrow

According to a recent study, it is possible that the spike protein of this variant was subjected to a strong positive selection compatible with host-jumping.22 Indeed, the mutations in the omicron RBD significantly overlapped with SARS-CoV-2 mutations known to promote adaptation to mouse hosts, particularly through enhanced spike protein binding affinity for mouse ACE-2. Thus, a tentative scenario could be that the ancestor of the omicron virus jumped from humans to mice, accumulated mutations, then jumped back into humans.23 According to this model, the mutational pattern of the omicron spike protein should not be interpreted as the result of a gradual improvement of SARS-CoV-2 for human host cells, but instead, as a series of compromises required for inter-species back and forth jumps.

In marked contrast with omicron, the delta variant is characterized by a concomitant and convergent evolution of the NTD and the RBD, leading to a remarkable adaptation for their respective targets (lipid raft and ACE-2) on human cell membranes. In this respect, it is interesting to mention that two routes of infection have been characterized for SARS-CoV-2: cell surface fusion, which requires S1-S2 cleavage by TMPRSS2 (route 1), and endocytosis, which is TMPRSS2-independent (route 2).15 The T-index adequately reflects the first route, as it takes into account the electrostatic surface potential that controls the binding of the virus to the host cell membrane.3 As expected, delta (T-index >10) is fourfold more efficient than omicron (T-index 3.90) to infect TRMPSS2-rich Calu-3 cells through route 1.15 On the contrary, omicron is 10 fold more efficient than delta to infect HEK cells which only support endosomal entry of SARS-CoV-2 (route 2).15 Overall, these data suggest that delta is optimized for fusion at the cell surface, whereas omicron gains entry through endosomal fusion. This specificity of the omicron variant, which is probably due to the geometric reorganization of the S1-S2 cleavage site of its spike protein (Figure 1A), is consistent with (i) a lower capacity to fuse infected cells to form syncytia, and (ii) a lower pathogenicity.

The mutations and indels located in the omicron NTD and RBD also dramatically affect key neutralizing epitopes,24,25 suggesting that current vaccines based on the original Wuhan strain will confer very little protection against this variant (Table 1 and Figure 2). In parallel, the facilitating epitope of the NTD29-31 is almost destroyed by the 3-amino acid insertion at position 214 (amino acid residues 215-216-217), further underscoring the lack of logic in this exacerbated mutational profile. However, even in absence of facilitating antibodies, sub-neutralizing antibodies may bind to the virus and mediate its entry into host cells by an Fc receptor-dependent mechanism.25 Therefore, the neutralizing antibodies elicited upon vaccination may at best not protect against the omicron variant25 but at worst facilitate its transmission through a classic antibody-dependent enhancement (ADE) mechanism. This hypothesis is supported by the high prevalence of omicron contaminations in vaccinated people, e.g. in Norway.24 In Marseille (France), we have already deposited 18 genomes in GISAID as of 16/12/2021 (out of 62 for France). Some of the cases were indeed in vaccinated patients. In addition, some correspond to secondary transmission, which was not observed for the first cases of infection with the Marseille-1 variant which had emerged in our region in July 2020.25

5 | CONCLUSIONS

This structural analysis of the omicron variant (B.1.1.529) may shed some light on the striking and unusual structural features that control the multiple facets of this newly emerging variant. According to the
target cell type, the omicron variant may be either less or more infectious than delta. Due to an inconsistent distribution of its electrostatic potential and to a defect in the S1-S2 cleavage, omicron is expected to be less pathogenic than delta. Further studies will be necessary to assess whether the ACE-2 receptor polymorphism could allow regional breakthroughs of omicron, especially in immunocompromised individuals.

An important question is whether omicron may increase in prevalence and become predominant in case of decreased incidence of delta as was the case for all previous variants to date a few months after their emergence, most probably because of the accumulation of noxious mutations. This may indeed be the case in South Africa, where omicron emerged at the time of a delta disappearance. In contrast, in Denmark, France, and UK, delta was still present when omicron started to spread. In this case, immune escape may facilitate an omicron breakthrough in vaccinated people, which may suggest that the omicron variant has a fitness advantage in presence of neutralizing antibodies generated against the original Wuhan spike protein. Whether these neutralizing antibodies may facilitate the infection by the omicron variant through an ADE mechanism remains to be established.

A limitation of the present analysis is that it compares a newly emerging virus to an old one that emerged several months ago. As a matter of fact, despite no clear virological advantage over delta, omicron might increase in prevalence and even become predominant, which has been the fate of all previous variants to date after a few months of circulation due to the accumulation of most often deleterious mutations. Finally, one should be aware that resistance to infection in the upper respiratory tract could be due preferentially to innate mucosal immunity and could not be assessed by measuring circulating antibodies in the blood that do not have access to these mucosal membranes.

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CONFLICT OF INTERESTS
Didier Raoult has a conflict of interest being a consultant for Hitachi High-Technologies Corporation, Tokyo, Japan from 2018 to 2020. All other authors have no conflicts of interest to declare. Funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

AUTHOR CONTRIBUTIONS
Jacques Fantini, Nouara Yahi, and Henri Chahinian: performed the molecular modeling studies. Bernard La Scola: performed the characterization of the omicron variant in cell cultures. Philippe Colson and Nouara Yahi: analyzed the genomic sequences and extracted the mutational patterns of SARS-CoV-2 variants. Jacques Fantini and Didier Raoult: designed the study and wrote the manuscript.

DATA AVAILABILITY STATEMENT
The authors confirm that the data supporting the findings of this study are available within the article.

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