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Antibodies targeting the spike protein of SARS-CoV-2 can be modified to increase their affinity for new virus variants

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Background. The accumulation of numerous mutations in emerging SARS-CoV-2 variants contributes to viral escape from immune response, necessitating an assessment of the effectiveness of known antibodies and consideration of their modification. **Methods.**The modeling of the receptor-binding domain (RBD) of wild-type (WT) SARS-CoV-2 S-protein complexed with the STE90-C11 antibody was conducted on the SWISS-MODEL server [1], based on the 7B3O structure [2] from the Protein Data Bank, while mutations in the S-protein and modifications of the antibody were performed with MODELLER 10.4 [3]. Molecular dynamics simulations of the resulting structures were carried out for 500 ns using GROMACS 2023.3 [4], followed by the calculation of binding free energy (ΔG) using the MM/PBSA method [5]. **Results.** The study modeled the RBD of WT virus complexed with the STE90-C11 antibody. A similar complex for the XBB.1.5 variant was derived by introducing 22 specific mutations in the RBD. The impact of all possible individual substitutions of interface amino acid residues in the antibody on the stability of the complex with XBB.1.5 was assessed, along with multiple substitutions. The most stabilizing set of substitutions was: V2I, A24E, V29F, R71M, V99F, A100F, and D101Y in the heavy chain; and A25F, S31Y, A50W, S56E, N92H, S93E, and P95E in the light chain. Three complexes were subjected to molecular dynamics simulations: RBD of WT virus with native STE90-C11, RBD of XBB.1.5 virus with native STE90-C11, and RBD of XBB.1.5 virus with modified STE90-C11. The average ΔG values over the last 100 ns of the trajectory were –56.41, –34.56, and –52.35 kcal/mol, respectively. **Conclusions.** The accumulation of mutations in the S-protein of emerging SARS-CoV-2 variants can potentially reduce the affinity of neutralizing antibodies. However, modifying amino acid sequences of antibody chains offers a promising strategy to re-establish efficient binding to the S-protein, thereby enabling the adaptation of antibodies in response to the virus's evolutionary changes.

Keywords: SARS-CoV-2, COVID-19, antibody, mutation, molecular dynamics, binding free energy.

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