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Molecular Dynamics and Bioinformatics Investigation of Spike Protein Mutations in SARS-CoV-2 from the Wuhan Strain to the XEC Variant

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Abstract

Since its emergence, SARS-CoV-2 has undergone significant evolutionary changes, particularly in the spike protein, resulting in the emergence of variants of concern (VOCs) such as Alpha, Beta, Gamma, Delta, and Omicron. Mutations in this protein have enhanced viral transmissibility, ACE2 receptor binding affinity, immune evasion, and pathogenicity, facilitating the global spread of new variants. This study aims to investigate the effects of recent mutations on the structure and dynamics of the SARS-CoV-2 spike protein using molecular dynamics (MD) simulations. Furthermore, the influence of these mutations on the spike protein's interactions with the ACE2 receptor and its antigenic properties is analyzed and evaluated.

MD simulations were conducted for the wild-type and mutant spike proteins in complex with the ACE2 receptor using GROMACS (version 2020.6). The CHARMM36 force field was employed for system parameterization, and each system was simulated for 100 nanoseconds. Structural stability, binding free energy, and conformational changes were analyzed to assess the impact of the mutations. Preliminary analyses indicate that certain mutations enhance the spike protein's binding affinity to ACE2 by stabilizing critical interface regions, while others facilitate immune evasion through alterations of surface-exposed epitopes. Dynamic analyses reveal changes in flexibility, stability, and structural dynamics, which are predicted to contribute to increased viral pathogenicity. Specifically, the XEC variant, a recombinant of KS.1.1 and KP.3.3, benefits from the rare T22N mutation (from KS.1.1) combined with Q493E (from KP.3.3), enhancing immune evasion and receptor binding.

The findings of this study provide a detailed molecular understanding of how spike protein mutations drive the emergence and spread of new SARS-CoV-2 variants. Therefore, this could enhance vaccine design and inform therapeutic strategies to combat future variants.

Key words: SARS-CoV-2, Spike Protein, Molecular Dynamics, Variants of Concern, Immune Evasion

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