Chapter 39
Homology Modeling and Evaluation of Sars-Cov-2 Spike Protein Mutant: D614G

Hima Vyshnavi
Accubits Invent Pvt. Ltd., India

Shahanas Naisam
Accubits Invent Pvt. Ltd., India

Aswin Mohan
Accubits Invent Pvt. Ltd., India

Suvanish Kumar
Accubits Invent Pvt. Ltd., India

Nidhin Sreekumar
https://orcid.org/0000-0001-9345-4471
Accubits Invent Pvt. Ltd., India

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), a global pandemic, affected the world, increasing every day. A mutated variant D614G, showing more virulence and transmission, was studied for forecasting the emergence of more virulent and pathogenic viral strains. This study focuses on structure modeling and validation. Characterization of proteins homologous to wild spike protein was done, and homology models of the mutated variant were modeled using these proteins. Validation of models was done using Ramachandran plot and ERRAT plot. Molecular dynamics simulation was used to validate the stability of the models, and binding affinity of these models were estimated by molecular docking with an approved antiviral drug. Docked complexes were studied and the best model was selected. Molecular dynamics simulation was used to estimate the stability of the docked complex. The model of 6VXX, a homologous of wild spike protein, was found to be stable with the interaction of the antiviral drug from this study.

DOI: 10.4018/979-8-3693-3026-5.ch039

INTRODUCTION

COVID 19 pandemic has spread across 180 countries from its source country China where the first human to human transmission was reported in December 2019 (Li et al., 2020; Wu et al., 2020). The pandemic agent is a coronavirus, named as "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" by the International Committee on Taxonomy of Viruses (ICTV) on 11 February 2020 (Lauxmann et al., 2020). SARS-Cov-2 infects the host cell with a positive single stranded RNA which is comparatively a large genome of ~30kb consisting of 9860 amino acids, 29891 nucleotides and 10 open reading frames (Wang et al., 2020). The viral genome codes for polyprotein 1a, polyprotein 1b, 16 non- structural proteins, and 4 main structural proteins: an envelope protein (E), spike protein (S), nucleocapsid protein (N) and membrane protein (M) (Guo et al., 2020; Hussain et al., 2005). Spike protein is the largest surface protein of SARS-Cov-2 virus and is a type1 membrane protein (Hoffmann et al., 2020). The attachment and entry of the SARS-Cov-2 virus to the host is mediated through S protein (Wu et al., 2020). S protein consists of an ecto-domain element, having 2 subunits, S1 and S2 (Shajahan et al., 2020). The S1 subunit has two subunits subdomains 1 and 2 (SD1 and SD2) and a Receptor Binding Domain (RBD) which will recognize and bind to the Angiotensin-Converting Enzyme 2 (ACE2) receptor (Wan et al., 2020) revealing the furin cleavage site on the S2 domain (Yan et al., 2020; Walls et al., 2020). Host cell proteases like TMPRSS2 initiate viral entry by acting upon the exposed cleavage site of the S2 domain (Li et al., 2020) by priming and activation cleavage mechanisms (Belouzard et al., 2009). The activation cleavage brings the viral membrane and host cell membrane in close proximity for viral fusion and entry (Li et al., 2020).

The rate and duration of infection within a selected population can alter the SARS-CoV-2 RNA genome with mutations that could potentially impact on its virulence and transmission (Timofeeva et al., 2020). A novel SARS-CoV-2 variant with a non-synonymous mutation D614G (aspartate to glycine at 614^{th} position) at the Carboxyl terminal region of SD2 (Becerra-Flores & Cardozo, 2020; Cortey et al., 2020) had enhanced the spike protein cleavage by proteases which increased transmission efficiency by limiting the shedding of S1 domain from the virion (Becerra-Flores & Cardozo, 2020; Zhang et al., 2020). It was observed that D614G mutation will lead to a change in the structure as well as type of interaction between the amino acids present in 613, 614, 615 positions and is followed by change in 3D structure of the protein, its orientation, finally resulting in functional changes. Due to this mutation, critical interprotomer hydrogen bonding from the S2 domain is disrupted and a shift is observed in the equilibrium between the open and closed states of S protein ectodomain (Johnson et al., 2020; Korber et al., 2020; Weissman et al., 2021). SD2 acts as an anchor that demarcates the movement of RBD as well as events like ACE2 receptor engagement and TMPRSS2 protease cleavage (Gobeil et al., 2021). In the evolution of coronaviruses to invade the host's immune system, spike proteins play a crucial role.

Homology modeling is a technique that is used to model three-dimensional structures of proteins (Zhang et al., 2020). The homology modeling we carried out in this work was based on the single amino acid change in the 614^{th} position of spike glycoprotein, aiming at identifying a suitable model structure for D614G mutant spike protein and to carrying out a comparative analysis between the existing wild spike protein and modeled structures (mutant models), which is completely a computational study.