Chapter 38
Homology Modeling and Binding Site Analysis of SARS-CoV-2 (COVID-19) Main Protease 3D Structure

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SAR-Cov-2) caused the coronavirus (COVID-19) pandemic. The global concern is the discovery of a new target drug for the total cure. Recently, some research showed that a few COVID-19 enzymes may have been contemplated to be potential drug targets, but not much is known about its structural biology. This research investigates the 3-D structure of protease SAR-CoV-2. The tertiary structure was determined by homology modeling. The Swiss-Model workspace and the basic local alignment search tool (BLAST) were employed for modeling, and the resulted model was validated with programs that include PROCHECK, Verify3D, and QMEAN to ascertain reliability. To establish the structures that fitted, HHBlits software was employed. To verify the structure quality, a Ramachandran plot was exploited. The binding site was determined using CASTp and DeepSite algorithms, which showed that this protein can be exploited as a prospective pharmaceutical target. Albeit further experimentation is required as a COVID-19 virus vaccine-design/target-drug.

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1. INTRODUCTION

The recent global outbreak disease called coronavirus 19 (COVID-19) with high sickness and death rates is induced by the severe acute respiratory syndrome coronavirus 2 (SAR-Cov-2). New distress from the Huanan seafood market, Wuhan, China, surfaced in December 2019 (Fox, 2020; Chellapandi, P., & Saranya, S.,2020). By 11 March, the world health organization (WHO) enunciated that the eruption was a pandemic, and by the 20$^{th\ of}$ July 2020, 14.6 million cases were affirmed in over 210 countries across the globe with 608 deaths. Nations such as the USA, Italy, and Germany have recorded more cases than China. To quickly coordinate the scientific and medical procedures to develop a cure, the WHO announces a state of a global health emergency (see- https://www.worldometers.info/coronavirus/). The world is craving vaccines, but little operative target drug has been feasible recently, and further investigation is ongoing. The pathogenesis techniques, transmission, and source of COVID-19 are still unknown, which impedes the investigation of working antiviral (Saranya, S.,2020). Nevertheless, one of the breakthroughs for this challenge is identifying the protease site of the SAR-Cov-2 and obstructing the metamorphoses that cause rapid transmission of the protection of the infected individuals. The immense investigations on COVID-19 genomics offer assurance of finding the vaccines to prevent and cure the virus.

Homology modeling is considered a vital technique in structural biology for reducing disparities between known protein sequences and experimentally determined structures. This includes the amino acid sequences of the interacting proteins, stoichiometry, and the whole structure of the complex. Many insights taken from the protein's 3D structure provide helpful information about their function from a molecular point of view and a wide range of applications in life science research. Although protein complexes are central to several cellular procedures, the entire quaternary structure is essential for the clear expression of the biological system.

In this work, the 3D structure of a SARS-CoV-2 (COVID-19) Main Protease bound to 2-Methyl-1-tetralone (PEPTIDE BINDING PROTEIN) (Guenther et al., 2020) is reported. Besides, the computer simulation of the prediction of its active site for a potential drug target is also provided.

2. MATERIALS AND METHODS

2.1 Computational Methods

The 3D modeling computational methods embroiled template selection, template alignment with the target, building model, and structure evolution. SARS-CoV-2 Main Protease sequence was fetched from the protein database (PDB) (Guenther et al.)- https://rcsb.org/structure/6ynq.

2.2. Searching for Template

BLAST and HHBlits were used for template searching in conjunction with the SWISS-MODEL template library (SMTL, last update: 2020-11-11, last included PDB release: 2020-11-06).

BLAST was engaged for the search for target sequence with the content of Amino acids in the SMTL and found 165 templates. The procedures listed in (Steinegger et al.) were used to build the initial HHblists profile, followed by one iteration of HHblits against Uniclust30 (von den Driesch et al.). The obtained profile has then been searched against all profiles of the SMTL. A total of 480 templates were found.