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Doctoral dissertation:

SARS-CoV-2: Antibodies and effect of non-structural proteins on protein synthesis in human ribosomes

Abstract:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causal agent responsible for the formidable global COVID-19 pandemic, officially declared by the World Health Organization in March 2020. Notably, the relentless pursuit of scientific endeavors has led to the development of numerous vaccines, pharmaceuticals, and immunotherapies, which have undoubtedly played an instrumental role in saving countless human lives. However, the fight against the COVID-19 pathogen continues, marked by the emergence of immune-evading variants of concern, such as the Delta and Omicron strains.

In an effort to develop more effective treatments and to understand the intricacies of adverse effects caused by vaccines and therapeutic agents, it is imperative to gain a deep understanding of the molecular interactions of SARS-CoV-2 with these interventions and the cellular constituents of the human body. Computational methods play a crucial role in improving the design of antiviral drugs, vaccines, and antibodies/nanobodies (Abs/Nbs) for the treatment of COVID-19. They are also essential for understanding complex processes such as membrane fusion, RNA splicing, messenger RNA (mRNA) translation, and protein trafficking, especially when SARS-CoV-2 non-structural proteins (NSPs) are involved in the ribosome. Computational approaches span the spectrum from all-atom to coarse-grained models, enabling a deeper understanding of these complex phenomena.

In this dissertation, three computational studies focus on SARS-CoV-2, pursuing two main objectives. First, we delve into the interactions of Abs and Nbs with the SARS-CoV-2 spike (S) protein. Second, we shed light on the impact of SARS-CoV-2 non-structural protein 1 (NSP1) on the protein synthesis process in the human ribosome. The dissertation consists of five chapters detailing these research endeavors.

Chapter 1 provides an introductory section covering key aspects, including the COVID-19 pandemic, the structure of SARS-CoV-2 and its variants, the life cycle of SARS-CoV-2, an overview of the interaction of Abs and Nbs with the S protein, and the interaction of NSP1 with the human ribosome.

Chapter 2 provides an overview of the computational methodologies used in the research presented in this dissertation. It includes a brief summary of the molecular dynamics simulations used to estimate the binding affinity of various SARS-CoV-2 biomolecular

complexes, such as steered molecular dynamics (SMD), umbrella sampling (US), and alchemical simulations.

Chapter 3 is dedicated to the interaction of Abs and Nbs with the receptor binding domain (RBD) of the SARS-CoV-2 S protein, where their binding affinity is assessed through all-atom SMD and coarse-grained US simulations. This chapter encompasses two separate research publications: In the first publication, the study revolves around the binding of REGN10933 Ab, REGN10987 Ab, and their combination to RBD. It is observed that REGN10933 exhibits a stronger binding affinity to RBD than REGN10987. Interestingly, the combination of REGN10933 and REGN10987 displays even stronger binding to RBD. The stability of REGN10933-RBD and REGN10933+REGN10987-RBD complexes is primarily governed by electrostatic interactions, whereas the stability of REGN10987-RBD depends on van der Walls (vdW) interactions. In particular, REGN10933 and REGN10933+REGN10987 show similar potency against the Delta variant and the wild type. However, they are less effective against the Omicron variant, confirming recent experimental results. The second publication examines the concurrent binding of H11-H4 Nb and CR3022 Ab to RBD, revealing a markedly increased binding affinity compared to their individual associations with RBD. The combination of H11-H4 and CR3022 increases the ability to neutralize SARS-CoV-2. The stability of the H11-H4-RBD complex is mainly driven by vdW interactions, while electrostatic interactions play a more significant role in the stability of CR3022-RBD and H11-H4+CR3022-RBD complexes. CR3022 is a promising candidate for the treatment of COVID-19, especially against the wild type strain. In addition, it is noteworthy that H11-H4 exhibits strong neutralizing capabilities against Alpha, Kappa, and the highly concerning Delta variants, consistent with recent experimental data.

Chapter 4 focuses on the interaction between mRNA and the 40S ribosome in the presence and absence of NSP1. Using all-atom SMD and coarse-grained alchemical simulations, our analysis revealed that mRNA exhibits significantly stronger binding affinity for the 40S-NSP1 complex compared to the 40S ribosome alone. These results are in close agreement with experimental observations. Furthermore, our studies showed that the electrostatic interaction between mRNA and the 40S ribosome plays a key role in driving the mRNA translation process. Upon entry into host cells, NSP1 can bind to the 40S ribosome, thereby interfering with the translation process.

Finally, Chapter 5 provides a summary of the findings presented in this thesis and outlines potential directions for future research.

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