Structural bioinformatics studies of viral proteins

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ABSTRACT

Hemorrhagic fever viruses (HFVs), such as filovirus, arenavirus, nairovirus, are zoonotic pathogens that often cause severe, life-threatening disease in human. There are only a few approved therapeutics for these viral diseases. Although it has been reported that some antiviral drugs such as nucleotide analogues clinically used for other viral diseases may also be beneficial against these viruses, their efficacies have not been fully proven and concerns about adverse effects remain. Thus, the development of effective and safe therapeutics against hemorrhagic fever viruses is of crucial importance.

The present work was designed with two broad research objectives. Firstly, we aimed to computationally predict and experimentally evaluate the functionally relevant sites required for replication of hemorrhagic fever viruses, particularly the Ebola virus (EBOV). Secondly, as a complement to the previous objective, we focused on the design of small compounds that could target these functional regions of viral proteins.

In order to predict protein interaction sites on viral proteins, we analyzed 3D structures of viral proteins by using patch analysis. We found a novel hydrophobic patch on the surface of the EBOV VP35 protein and predicted that this patch is a functionally important site. Although the functionally important sites on viral proteins might be potential targets for antiviral drug discovery, most of these sites are likely to be engaged in protein-protein interactions (PPIs). Generally, targeting PPIs with small molecules is challenging, since protein–protein interfaces are relatively large, flat areas (1500–3000 $Å^2$). In this study, we explored the suitability of using small compounds to inhibit PPIs in viral proteins using several computational approaches. Druggable sites, or sites engaged in PPIs, on EBOV proteins were predicted using a combination of patch and cavity analyses. One site on VP35 was selected as a target for antiviral drug discovery. The other method, mixed solvent molecular dynamics simulation, confirmed the druggable site on VP35. We then performed *in silico* screening of 5,597 compounds from DrugBank, and the top-ranked compounds were selected for an *in vitro* assay. In this presentation, we will discuss the results obtained through our current analyses.

REF.

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