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Mosquito-borne viruses: A computational search for antiviral drugs

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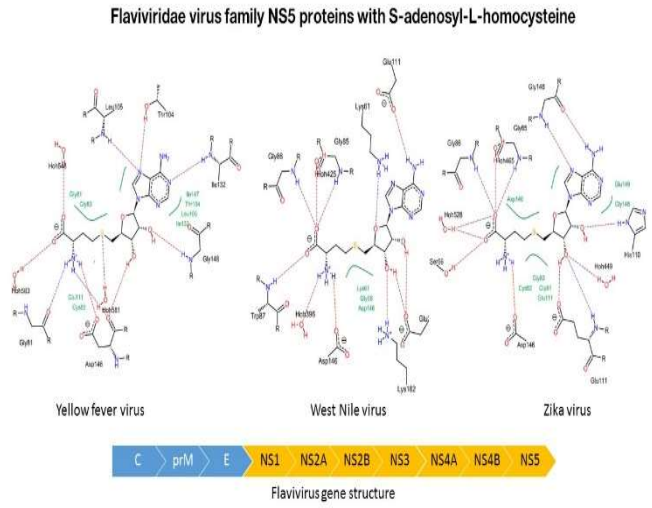
Graphical Abstract



Abstract.

Mosquito-borne viruses of Flaviviridae virus family are dangerous for human. To develop drugs and vaccines against Flaviviridae viruses, promising targets must be identified.The genomes and biochemistry of Yellow fever (YFV), West Nile (WNV), and Zika (ZIKV) viruses are similar. Therefore, the main aim of this project was to identify lead compounds which could simultaneously inhibit all three viruses targeting one or more viral proteins.

Introduction

Mosquito-borne viruses of Flaviviridae virus family are dangerous for human [1]. To develop efficient drugs and vaccines against Flaviviridae viruses, promising protein targets must be identified. The genomes and biochemistry of Yellow fever (YFV), West Nile (WNV), and Zika (ZIKV) viruses are similar [2]. Therefore, the main aim of this project was to identify lead compounds which could simultaneously inhibit all three viruses targeting one or more viral proteins. Activation of non-structural proteins NS1, NS2A, NS3 and NS5 inside of mosquito-borne viruses is necessary for virial replication, as well as structural envelope E is responsible for entry of viral particles into the cell. Hence, the inhibition of at least one type of protein could neutralize the entire virus.

Materials and Methods

At the first step, RCSB Protein Data Bank was used to extracted data on sequences variations for target proteins [3]. Next, Basic Local Alignment Search Tool (BLAST) tool was applied to find similarity between studied proteins of YFV, WNV, and ZIKV [4]. A series of FDA approved drugs from Binding database (https://www.bindingdb.org) and DrugBank (http://www.drugbank.ca/drugs) were screened [5,6]. Selected proteins were prepared for molecular docking: native ligand and waters

were removed, and polar hydrogens were added to the protein.The active sites of the enzymes were defined to include residues within 8.5 Å radius around inhibitor. Both crystallography-based and suggested allosteric sites were considered for docking. Final scores were used for database ranking.The best pose with the highest score was selected to analyze the interactions between ligand and protein. At the next step, hits were used as references for deeper screening of ZINK database [7]. Results were compared with literature data. Docking, scoring, and screening procedures were performed using BioSolveItsuite [8].

Results and Discussion

Ten target proteins were extracted from RCSB: structural envelope (E), non-structural hydrolase and transferase for YFV, non-structural hydrolase and methyltransferase for WNV and non-structural methyltransferase, helicase, protease RNA-dependent polymerase and structural envelope for ZIKV. These proteins contained bonded ligands, so locations of these ligands were used as a reference for initial search of possible binding pockets. In addition to it, allosteric sites were analyzed.

While genomes of YFV, WNV, and ZIKV are quite similar, the qualitative analysis based on BLAST revealed, that the best binding sites for promising hits were located in different places for same types of proteins. In some cases, these differences are drastic. For instance, similarities between non-structural NS1 proteins were: ~ 55 % for ZIKA and DENV, ~50 % for ZIKA and YFV, ~ 55 % for ZIKA and WNV, ~ 45 % for YFV and DENV, ~ 45 % for YFV and WNV, and ~ 50 % for DNV and WNV.

Molecular docking was performed for more than 6000 drug-like compounds.Free energies of binding varied from −35 kJ/mol to -6 kJ/mol for hits.A series of compounds were identified as inhibitors for proteins of certain type. For example, quinacrine and its derivatives acted in the same way against all nonstructural NS3 proteins. Other examples are nanchangmycin and lovastatin, that interacted with allosteric sites of NS2A and NS3 proteins. Specific poses were identified and analyzed. For instance, in the case of Zika, selected drugs mainly bonded to Glu234, Gln396, and Glu 231 inside of NS3 protein.

References

[1]Vlachakis D (2008)The Flaviviridae Viral Family: Properties and Genome Bank.

[2]Morales M A,FabbriCM, ZuninoG E, KowalewskiM M, et al. (2017) Detection of the mosquito-borne flaviviruses, West Nile, Dengue, Saint Louis Encephalitis, Ilheus, Bussuquara, and Yellow Fever in free-ranging black howlers (Alouattacaraya) of Northeastern Argentin. PLoSNegl Trop Dis 11(2): e0005351.

[3]RCSB Protein Data Bank, https://www.rcsb.org

[4]Basic Local Alignment Search Tool, https://blast.ncbi.nlm.nih.gov/Blast.cgi

[5]Binding database,https://www.bindingdb.org

[6]DrugBank,http://www.drugbank.ca/drugs

[7]ZINK database, http://zinc.docking.org/

[8] Rarey M, Kramer B, Lengauer T, Klebe G (1996) A fast flexible docking method using an incremental construction algorithm. J MolBiol 261: 470–489