Structure-based discovery of potential small-molecule inhibitors targeting Zika virus NS3 helicase

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Abstract

Zika virus (ZIKV) is a mosquito borne pathogen that has been rapidly a rapidly expanding epidemic across Central and South America since 2015. It belongs to flavivirus family and is closely related to Dengue virus and West Nile virus. ZIKV was first isolated in 1947 from a rhesus monkey around the Zika forest of Uganda. ZIKV has been realized as a major health risk, making it a compelling target for viral therapeutics. Its infection causes not only mild symptoms such as fever, headache, arthralgia and conjunctivitis, but frightening neural diseases including Guillain–Barré syndrome, congenital microcephaly, as well as macular atrophy. There's an urgent need to discover and develop direct-acting antiviral agents (DAAs) in view of the current lack of effective medicine for ZIKV. Nonstructural protein 3 (NS3) helicase of ZIKV is considered to be essential for viral replication and have become an attractive target for the development of DAAs. Recent years, in silico virtual screening has been generally accepted as a rapid, efficient, economical approach with low time and labor cost for screening a large set of compounds. Here, an in-silico screening analysis of NCI diversity dataset with ZIKV NS3 protein targets has been carried out using a structure-based molecular docking approach. A total of 1974 compounds with structural simplicity and diversity have been docked. Top-ranked 5% of compounds with drug-like properties were selected for antiviral evaluation by cell-based ZIKV infection assays. Three hits were identified to specifically inhibit the viral infection with EC50 values at a micro-molar level. Different series of potential derivatives with expected better antiviral activities were presented based on similarity search and target-ligand binding modes. Overall, the discovery of these NS3-targeting compounds may serve as novel leads for further optimization and development of clinical ZIKV inhibitors.

Image

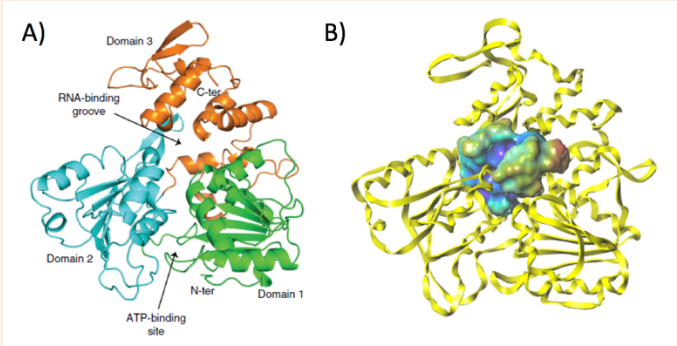


Fig 1| A) crystal structure of ZIKV NS3-HEL (AUG 2016, FEMS Microbiology Letters). B) diagram of the docking protomol generated according to the RNA-binding groove.

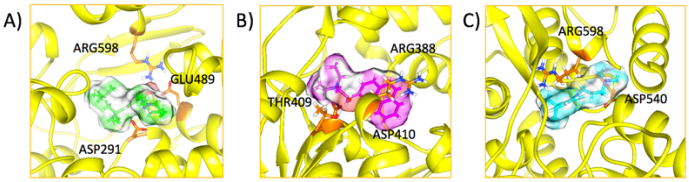


Fig 2| molecular docking demonstration of the predicted ZINV NS3-HEL-hit compound binding modes and critical interacting residues. Three hit molecules Compound 01, 02, 03 (shown in green, magenta, and cyan respectively) inside the NS3-HEL catalytic center are presented with interacting residues (shown in orange).

Recent Publications

1. Systematic Reconstruction of Molecular Cascades Regulating GP Development Using Single-Cell RNA-Seq. Cell Rep. 17;15(7):1467-80. 2016.
2. Discovery of novel CXCR4 antagonists using an integrative structure- and ligand- based virtual screening, The 1st SABPA Frontiers in Therapeutics and Diagnostics Forum, 2017 Feb.

Biography



Siyu Zhu has been a PhD student at Tsinghua University since 2014. She has her expertise in virtual screening and rational design of antiviral drug discovery. Her educational background of biotechnology at Fudan University enabled her to understand the importance of biological and medical research as well as how to align technologies to practical applications. She was ranked second in her major and graduated as Bachelor of Science (cum laude). In order to achieve further scientific training, she started her Ph.D. program and won a Future Scholar Research Fellowship of Tsinghua University. She is currently concentrated on the research of bio-molecular interactions and drug design related to HIV co-receptor CXCR4 as well as ZIKV nonstructural proteins using multiple approaches such as molecular biology, chemical biology and computer-aided drug design.

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Notes/Comments