Zika Virus Helicase: From biophysics to drug discovery of a moving target

A Thesis

Submitted

by

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Dedicated to my loving Parents

Declaration by the Research Scholar

I hereby declare that the entire work embodied in this Thesis entitled "**Zika virus NS3 helicase: From biophysics to drug discovery of a moving target**" is the result of investigations carried out by me in the ***School of Basic Sciences,*** Indian Institute of Technology Mandi, under the supervision of ***Dr. Rajanish Giri,*** and that it has not been submitted elsewhere for any degree or diploma. In keeping with the general practice, due acknowledgements have been made wherever the work described is based on finding of other investigators.

IIT Mandi (H.P.) Signature:

Date: **Deepak Kumar**

Declaration by the Research Advisor

I hereby certify that the entire work in this Thesis entitled "**Zika virus helicase: From biophysics to drug discovery of a moving target**" has been carried out by ***Deepak Kumar,*** under my supervision in the ***School of Basic Sciences,*** Indian Institute of Technology Mandi, and that no part of it has been submitted elsewhere for any Degree or Diploma. In keeping with the general practice, due acknowledgements have been made wherever the work described is based on finding of other investigators.

IIT Mandi (H.P.)

Date:

Signature:

Dr. Rajanish Giri

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Abstract

For almost sixty years, Zika virus (ZIKV) disease was considered as one of the neglected tropical diseases, and therefore little is known about ZIKV. In recent years, the repeated outbreaks of ZIKV have been reported throughout the world from Americas, South Pacific, and South Asia. The real danger posed by ZIKV is neurological defects like microcephaly and Guillain-Barre syndrome in new-borns as well as in adults, respectively. Epidemiological studies have also reported the sexual mode of ZIKV transmission further raising the threat alarm worldwide. As on 1st February 2016, the World Health Organization has called the global health emergency that demands the development of safe and effective therapeutics.

Moreover, India has also witnessed the ZIKV outbreak in 2018 in western states where more than 500 cases of ZIKV were observed. Also, this is pointless to mention the high-risk status of ZIKV infection in India remains a massive threat due to favourable geographical and environmental conditions needed for the growth of vector, Aedes mosquitoes. Therefore, the lack of specific antivirals against ZIKV demands to search for Zika specific therapeutics by understanding the different aspects of pathogenesis to fight against future outbreaks. ZIKV hijack the host systems with a minimal set of proteins (only ten). These small set of proteins have vast multifunctional diversity which could be understood well by higher propensity of intrinsically disordered proteins (IDPs) regions in viral proteomes as shown in literature. Despite being disordered, IDPs are functionally capable, hence, breaking the classical paradigm of structure-function. In this thesis, we have designed our study first to find out the penetrance of IDPs in the whole proteome of ZIKV. After that, we have found the significant involvement of IDP regions in functioning of ZIKV NS3 helicase protein which is essential for replication.

Further, ZIKV NS3 helicase was studied to establish its folding-functions relationships under different physiological conditions. A novel cofactor NS4A protein was reported to stimulate the activity of ZIKV NS3 helicase. Also, the NS3 helicase was studied for inhibitor design purpose by using structure-based drug designing approaches, molecular dynamics simulations and in-vitro inhibition assays. Overall, this study of ZIKV NS3 helicase could be implicated in understanding viral pathogenesis.

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