Zika Virus: Role of Envelope protein in entry and therapeutics

A Thesis

Submitted

by

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Dedicated to my loving
Grandmother and Parents

Declaration by the Research Scholar

I hereby declare that the entire work embodied in this Thesis entitled "**Zika Virus: Role of Envelope protein in entry and therapeutics**" 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: **Nitin Sharma**

Declaration by the Research Advisor

I hereby certify that the entire work in this Thesis entitled "**Zika Virus: Role of Envelope protein in entry and therapeutics**" has been carried out by ***Nitin Sharma,*** 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

Flaviviruses are amidst the leading class of human pathogens causing millions of infections every year throughout the world. Rapid progress in structural biology has improved the understanding of flaviviral pathology in last few years. Zika virus (ZIKV) is an emerging flavivirus that has recently shown its largest outbreaks in different parts of the world leading to severe neurological disorders. A wide variety of cells are found to be permissive for ZIKV that can sustain in extreme pH variations of blood, saliva, urine, semen, testis, vagina, cerebrospinal fluid and various other body fluids. In order to successfully infect a suitable host, a virus must attach to the host's extracellular surface and penetrate the cytosol. ZIKV entry into the host cells was examined to be progressed by receptor-mediated endocytosis. Envelope (E) protein is primarily responsible for receptor binding and leads to endosomal uptake by the host cells. The understanding of E protein conformational transitions will provide the insights into the mechanism of pathogenesis and illuminate the specificity of Zika virus tropism. Therefore, we have studied the conformational flexibility and structural stability of ZIKV E protein in different physiological conditions to distinguish its role in virion survival. Further, we have analysed the conformational stability of ZIKV envelope protein domain III (EDIII). The discovery of aggregation propensity of ZIKV EDIII introduced new insights for implications towards vaccine development process. Further, we have identified an important small molecule inhibitor binding site that may interrupt the conformational rearrangement of ZIKV E protein during viral entry. The discovery of specific inhibitors of Zika virus entry will improve the drug development process and will be helpful to mankind. Hence, using docking and MD simulations studies, we have discovered a few important inhibitors of E protein that can restrict the conformational dynamics to block the entry of ZIKV. And, F1065-0358 was experimentally validated to inhibit the proliferation of ZIKV in Vero cells possibly by targeting E protein.

Contents