Article

Open Reading Frame 4 protein as potential drug target for HEV: Structural evaluation through computational approaches

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Received 21 May 2023; *Accepted 28 June 2023*; *Published online 20 July 2023*; *Published 1 March 2024*

Abstract
Hepatitis E virus (HEV) is the main cause of acute hepatitis worldwide. The viral infection caused by G1 HEV in pregnant women has become a major health concern in the past few years. The mechanism underlying the pathogenesis of viral infection in HEV G1 isolates is attributed to four different open-reading frames (ORFs) i.e., ORF1, ORF2, ORF3 and ORF4. The present analysis has considered ORF4 protein as the molecular target due to its intrinsic disorder propensity. Intrinsically disordered regions (IDRs) are regions in proteins that do not possess stable secondary and tertiary structure and are prevalent in eukaryotes. IDRs are found to be closely associated with numerous human diseases, for instance, Parkinson and Alzheimer disease. The extreme flexibility and random coiled conformations of IDR allow it to undergo protein-protein interaction (PPI). The 3-dimensional (3D) structures of the target protein were designed using homology modelling algorithms. The generated models were assessed through structure verification tool PROCHECK. In this paper, we provide an overview of ORF4 protein structure–function relationship and its involvement in several biological processes through PPIs. Our results suggest that ORF4 protein has the potential to act as drug molecule, thus can accelerate the process of drug designing strategies against HEV.

Keywords Open Reading Frame 4; intrinsically disordered region; drug target; secondary structure; 3D model.

Network Biology
ISSN 2220-8879
URL: http://www.iaees.org/publications/journals/nb/online-version.asp
RSS: http://www.iaees.org/publications/journals/nb/rss.xml
E-mail: networkbiology@iaees.org
Editor-in-Chief: WenJun Zhang
Publisher: International Academy of Ecology and Environmental Sciences

1 Introduction

Hepatitis E virus (HEV) is the major aetiological agent of Hepatitis E, also called enteric hepatitis (enteric means related to the intestines) infection. Worldwide, about 20 million HEV infections and 3.3 million symptomatic hepatitis E cases occur annually which results in 44,000 deaths (Hoofnagle et al., 2012; Kamar et al., 2017; Wedemeyer et al., 2012). HEV is a quasi-enveloped *Orthohepevirus*, with a single-strand, positive-sense RNA genome of around 7.2 kb in length and flanked with short 5′ and 3’ non-coding regions (NCR) (Meng, 2008; Mushahwar, 2008). Recently, a novel reading frame ORF4 has been identified in G1 of HEV entirely embedded within ORF1 in a different reading frame (Nair et al., 2016; Subramani et al., 2018).

Dyson HJ, Wright PE. 2005. Intrinsically unstructured proteins and their functions. Nature Reviews Molecular Cell Biology, 6(3): 197-208

Fuertes G, Nevola L, Esteban-Martín S. 2019. Perspectives on Drug Discovery Strategies Based on IDPs. Intrinsically Disordered Proteins. 275-327, Academic Press, USA

Shafat Z, Tazeen A, Ahmed M, Parvez MK, Parveen S. 2021c. Understanding Hepatitis E viruses by exploring the structural and functional properties of ORF4. Network Biology, 11(4): 274-276

Metallo SJ. 2010. Intrinsically disordered proteins are potential drug targets. Current Opinion in Chemical Biology, 14(4): 481-488

Mbarek A, Moussa G, Leblond Chain J. 2019. Pharmaceutical applications of molecular tweezers, clefts and clips. Molecules, 24(9): 1803

Marques SM, Daniel L, Buryska T, Prokop Z, Brezovsky J, Damborsky J. 2017. Enzyme tunnels and gates as relevant targets in drug design. Medicinal Research Reviews, 37(5): 1095-1139

Coleman RG, Sharp KA. 2006. Travel depth, a new shape descriptor for macromolecules: application to ligand binding. Journal of Molecular Biology, 362(3): 441-458

Brezovsky J, Kozlikova B, Damborsky J. 2018. Computational analysis of protein tunnels and channels. Methods in Molecular Biology, 1685: 25-42