INTERACTION OF EBOLA VIRUS WITH INNATE AND ADAPTIVE IMMUNE SYSTEM: AN *IN SILICO* STUDY

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ABSTRACT

Objective: Ebola virus (EBOV) is an extremely pathogenic, that can cause severe hemorrhagic fever in human with case fatality rates of up to 90% for which no vaccine or treatment is currently available. The mechanism underlying this lethal outcome is still unclear. However, an alteration of the immune responses represents one of the most important pathogenic mechanisms of Ebola virus infection. EBOV encodes two different proteins (VP24 and VP35) that block the induction of immune responses. Thus, we explored the potential interaction of Ebola virus proteins (VP24 and VP35) with the Toll-like receptor and MHC-1 receptor.

Methods: The interaction of Ebola virus protein towards immune system has been checked by Cluspro 2.0.

Results: Our results indicated that the Ebola Virus proteins (VP 24 and VP 35) have good interaction towards the Toll-like receptor (TLR-3) and MHC-1 which are a crucial component of innate and adaptive immune system.

Conclusion: The findings of this study will be helpful for researchers to design drugs or vaccines for the treatment/prevention of EBOV infections.

Keywords: Ebola Virus, Innate Immune system, Adaptive Immune system

Ebola virus (EBOV) is belonging to "Filoviridae" family of negative-sense RNA viruses. It can cause severe hemorrhagic fever leading up to 90% lethality [1]. This virus is first recognized near the Ebola River valley during an outbreak in Zaire in 1976 [2-4]. In the year of 2014, Ebola epidemic was the largest in the history that affected people in many West African countries. The lethal cases of EBOV infections show signs of an impaired innate and adaptive immune response [5, 6].

The innate immune system utilizes conserved receptor system as a sensor of foreign microbial components as well as products of damaged or inflamed self-tissues. Examples of such a receptor system include toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-1 like receptors (RLRs). TLRs are widely expressed in many cell types such as macrophages, neutrophils and dendritic cells [7, 8]. Viruses are mainly recognized by TLR3 which results in the MyD88-independent activation of IRF3, a key transcription factor necessary for interferon production, which leads to the destruction of viruses. In many of the viral infections, an early action of cytokines produced by infected cells and dendritic cells is not sufficient to eliminate the pathogen [9]. In such instances, an adaptive immune response is activated to ensure host survival. Recently, Xu *et al.*, 2014 demonstrated that Ebola virus proteins (VP 24 and VP 35) actively antagonize STAT1 signaling to counteract the antiviral effects of interferons [10].

Major histocompatibility complex (MHC) class I molecules are found on nearly every nucleated cell of the body. MHC can display peptide fragments of viral proteins to the cytotoxic T cells. Therefore, the cytotoxic T cells eliminate the viral infected cells by the selections of various cytokines. Unfortunately, there are many viruses which evolved the various proteins that can interfere with this process and results in the failure of adaptive immunity. The Ebola virus is the one of them, which produces two major viral proteins (VP 24 and VP 35) which can inhibit the MHC recognition process.

Literature has shown that EBOV alters both the innate and adaptive immune response signaling pathways through an unknown mechanism [5]. Thus, the present investigation has been explored an interaction of Ebola viral proteins (VP24 and VP 35) with TLRs and MHC-1.

To investigate the interaction of Ebola viral proteins (VP24 and VP 35), computational analysis was carried out on a Red Hat 5.0, Linux platform running on a Dell Precision workstation with Intel core 2 quad processor and 8 GB of RAM. The x-ray crystal structure of Ebola viral VP 35 (PDB: 3L2A) and VP 24 (PDB: 4M0Q) with resolution 1.71 A°, 1.92 A°, *R*-value: 0.173 (obs.), 0.211 (obs.); human toll like receptor (PDB: 1ZIW) and MHC-1 (PDB: 3AM8) wit h resolution 2.10 A°, 1.71 A°, R value:0.210, 0.191 (obs) respectively,were obtained from the protein data bank (Research Collaboratory for Structural Bioinformatics(RCSB) http://www.rcsb.org/pdb).The proteins (PDB:4M0Q, 3L2A, 3AM8 and IZ1W) were prepared by using the Protein Preparation Wizard (Shcrodingers LLC). The chain A of all proteins were selected for the protein-protein docking protocol using Cluspro 2.0. Among the results obtained from Cluspro 2.0, the docked protein models with lowest energy with higher number of clusterings were selected to study the protein-protein interactions with help of Shcrodingers LLC.

The TLR binding site contains the important residues Asp 36, Ser 38, Asp 81, Asp 153, Glu 175, Lys 201, Asn 252, Tyr 383, His 359 and Glu 434. The docking of Ebola virus VP35 protein (Lys 323, Arg 301, Arg 311, Lys 271, Glu 251, Tyr 207, Asn 243 and Asp 246) showed good interactions with the amino acid of Toll-like receptor as shown in fig. 1.
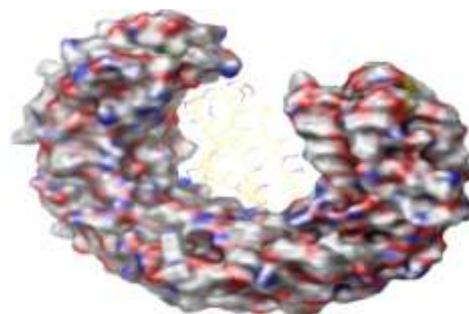

Fig. 1: Interaction of Ebola virus (VP35) with toll-like receptor

The different amino acids of Ebola virus VP35 (Asp 278, Asn 243, Glu 251, Asp 246,Gln 283, Glu253 and Asp 219) also showed good

interaction towards MHC 1 receptor amino acid residues (Arg 17, Arg 21,Asp 119, Thr 94,Gln96,Arg 48,Arg 35,Arg 48,Tyr 27 and Arg 234) as shown in fig. 2.
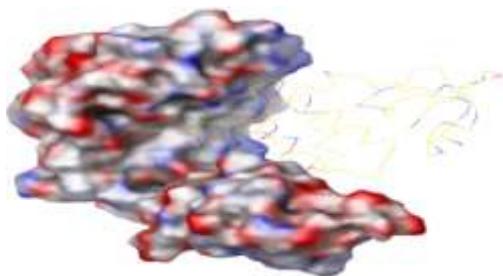

Fig. 2: Interaction of Ebola virus (VP35) with MHC-1

Ebola virus VP24 binds with ten different amino acid residues (Glu 203, Asn 253, Ser 205, Ser 282, Lys 330, Lys 416, Arg 484, Lys 619, Arg 643 and Asn 662) of the toll-like receptor as shown in fig. 3.
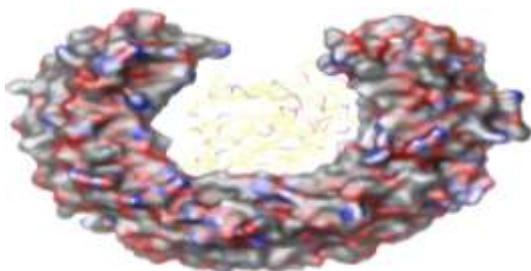

Fig. 3: Interaction of Ebola virus (VP24) with toll-like receptor

In case of MHC-1, ebola virus VP 24 protein interacts with four different residues (Glu 232, Glu 229, Arg 48 and Glu 237) as shown in fig. 4.
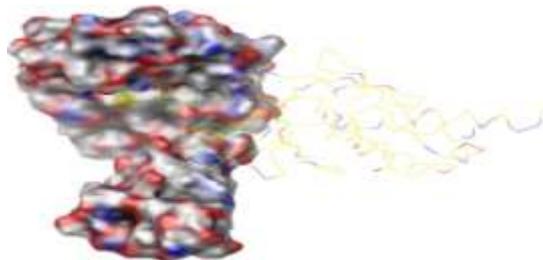

Fig. 4: Interaction of Ebola virus (VP24) with MHC-1

In conclusion, these results demonstrated that Ebola virus proteins (VP35 and VP24) have a good binding affinity towards human Toll-like receptor and MHC-1, which plays a key role in innate and adaptive immunity.

CONFLICT OF INTERESTS

Author declares no conflict of Interest

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