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Opinion

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Does disruption of integrins play a role on ebola virus hemorrhagic fever syndrome?

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Abbreviations: EHF, Ebola Virus Hemorrhagic Fever; VP35, Virus Protein 35 Kilodaltons; RGD, Arg Gly-Asp; KGD, Lys Gly Asp

Opinion

Ebola hemorrhagic fever (EHF) is caused by Ebola virus,[1] which belongs to the *Filoviridae* Family.[2] With 28,657 suspected cases and 11,325 deaths reported (WHO data), EHF is one of the most fatal infectious diseases.[3] Ebola hemorrhagic fever is characterized by cutaneous hemorrhages on skin, mucus membranes and visceral organs.[4] The factors involved in the pathogenesis of Ebola virus hemorrhagic fever are not completely understood. Several groups have reported possible explanations for the fatal hemorrhages observed in the infected patients. These include activation of endothelial cells followed by destruction of the barrier function.[5] enhanced production of inflammatory cytokines such as TNF alpha or Nitric Oxide.[6] destruction of cell membrane.[7] due to seleno-cystiene deficiency.[8] increased tissue factor expression.[9] In addition, viral glycoproteins are also thought to play a role in the pathogenesis of EHF.[10]

Heterodimeric receptors of the beta1 and beta3 integrin families are shown to play an important role in platelet adhesion and aggregation, which is critical for homeostasis and thrombosis.[11] In particular, GPIIb/IIIa integrant complex on platelets binds to collagen, fibrinogen and Von Willebrand Factor, resulting in platelet activation. This activation triggers the coagulation cascade resulting in blood clot formation and hemorrhage control. Ebola virus glycoprotein's (GP) are shown to interact with Integrins (beta1) and may be involved in the virus entry. Ebola GP expression also led to the down regulation of integrins.[12] Integrand αV was required for efficient GP-mediated transduction and EBOV infection of macrophages.[13] Binding of Ebola virus GP to aVbIII integrins is also shown to prime the endosomal cathepsins, a necessary step in the Ebola virus entry.[14]

VP35 protein (required for viral transcription) of Ebola virus contains RGD (Arg-Gly-Asp) and several RGD like motifs in the Table 1. Interestingly, RGD/KGD peptide motif is a conserved feature of low molecular weight non-enzymatic proteins called as "disinterring" present in snake venoms.[15] These molecules bind to the platelet surface integrins (such as alphaII-beta3), blocking the interaction of the platelets with the natural substrates such as fibrinogen and von Willebrand factor. This blockage results in potential inhibition of platelet aggregation.[16] (and thus preventing fibrin clots), a crucial step in homeostasis. Due to the presence of conserved RGD and RGD like motifs in VP35, it is possible that VP35 protein might potentially block/delay platelet aggregation. Delayed platelet aggregation might inhibit blood clotting in response to vascular injury/altered vascular barrier observed in the Ebola virus infected patients, thus exacerbating hemorrhages. Significantly decreased platelet aggregation observed in experimentally infected rhesus macaques supports this theory.[17]

Table 1 Arg-Gly-Asp (RGD) and similar motifs present in the VP35 protein of Ebola virus (Accession number AAM76032) with the amino acid residue numbers are shown in the figure. Amino acids are represented by single alphabets according to the standard nomenclature

	Sequence
RGD motif	297 Irsrgdipr 305
	185 Iesrdetvp 193
RGD like motif	266 Slaegdspq 274
	318 Kidrgwvcv 327

Presence of antibodies directed against VP35 in the serum of infected patients.[18] further suggests the existence of VP35 in the serum available for interaction with the platelets to exert this phenomenon. It is also interesting to note that the RGD sequence motif in VP35 is conserved between the different isolates of Ebola viruses (Sudan, Zaire and Reston). Despite these circumstantial evidences, experimental proof to demonstrate the disinterring like activity of VP35, GP and their roles in blocking/delaying the platelet aggregation still needs to be.[19] generated. Presence of RGD/RGD like motifs in the VP35 protein of Ebola virus raises the possibility of its role in exacerbation of the hemorrhagic syndrome, in addition to other factors already described in literature such as the binding of GP to integrands, elevated inflammatory cytokines, compromised vascular barrier etc. Future research, in this aspect might reveal definitive role of VP35 and glycoprotein's in the inhibition of platelet aggregation and pathogenesis of Ebola virus. Understanding the Ebola virus pathogenesis will enable design and development of efficient therapeutic strategies against hemorrhagic fever syndrome of Ebola virus.

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Conflicts of interest

None.

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