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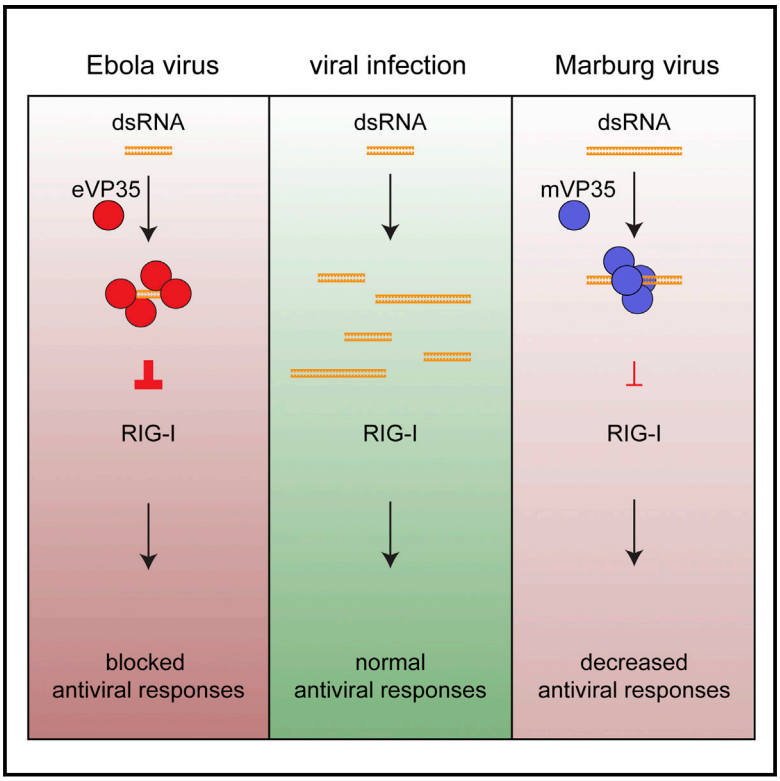
Differential Regulation of Interferon Responses by Ebola and Marburg Virus VP35 Proteins

Graphical Abstract



Highlights

- Ebola and Marburg viruses regulate interferon responses to different extents
- Ebola and Marburg VP35 proteins block RIG-I signaling with different efficiencies
- Ebola and Marburg VP35s have different binding modes and affinities for dsRNA
- Ebola virus VP35 caps the ends of dsRNA for superior RIG-I suppressing function

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In Brief

Edwards et al. demonstrate that although the VP35 proteins of both Ebola and Marburg viruses function to suppress RIG-I signaling and block interferon α/β production, Ebola virus is a more potent inhibitor of the response. This is due, in part, to more efficient RNA recognition by Ebola virus VP35.

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Differential Regulation of Interferon Responses by Ebola and Marburg Virus VP35 Proteins

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SUMMARY

Suppression of innate immune responses during filoviral infection contributes to disease severity. Ebola (EBOV) and Marburg (MARV) viruses each encode a VP35 protein that suppresses RIG-I-like receptor signaling and interferon-α/β (IFN-α/β) production by several mechanisms, including direct binding to double stranded RNA (dsRNA). Here, we demonstrate that in cell culture, MARV infection results in a greater upregulation of IFN responses as compared to EBOV infection. This correlates with differences in the efficiencies by which EBOV and MARV VP35s antagonize RIG-I signaling. Furthermore, structural and biochemical studies suggest that differential recognition of RNA elements by the respective VP35 C-terminal IFN inhibitory domain (IID) rather than affinity for RNA by the respective VP35s is critical for this observation. Our studies reveal functional differences in EBOV versus MARV VP35 RNA binding that result in unexpected differences in the host response to deadly viral pathogens.

INTRODUCTION

Zaire ebolavirus (EBOV) and *Marburg marburgvirus* (MARV) are members of the *Filoviridae* family of negative sense single stranded RNA (ssRNA) viruses and cause highly lethal hemorrhagic fever in humans (Bray and Murphy, 2007). The virulence of filoviruses is due in part to the potent inhibition of the innate immune system (Basler and Amarasinghe, 2009; Messaoudi and Basler, 2015). Although both EBOV and MARV inhibit the production of interferon (IFN)-α/β and the ability of cells to respond to IFNs, the mechanisms of inhibition differ. For example, the EBOV VP24 protein inhibits IFN-induced Jak-STAT signaling by blocking karyopherin alpha mediated nuclear accumulation of tyrosine phosphorylated STAT1, whereas MARV VP40 prevents STAT protein tyrosine phosphorylation (Mateo et al., 2010; Reid et al., 2006, 2007; Valmas and Basler, 2011; Valmas et al., 2010; Xu et al., 2014).

EBOV VP35 (eVP35) and MARV VP35 (mVP35) also block IFN production by binding double stranded (ds)RNAs through the C-terminal IFN inhibitory domain (IID) and prevent retinoic-acid inducible gene-I (RIG-I)-like receptor (RLR) activity (Albariño et al., 2015; Cárdenas et al., 2006; Hartman et al., 2006; Leung et al., 2010a; Prins et al., 2010; Ramanan et al., 2012; Yen et al., 2014). Mutation of VP35 residues critical for dsRNA binding results in increased IFN-α/β responses, reduced viral replication, and attenuation of EBOV in animal models, demonstrating the importance of VP35 as a virulence determinant (Hartman et al., 2008; Prins et al., 2010). Despite functional and structural similarities, comparison of the crystal structures of eVP35 and mVP35 IIDs in complex with dsRNA suggests differences in how eVP35 and mVP35 interact with dsRNA. Specifically, eVP35 interacts with the phosphodiester backbone and caps the ends of dsRNA (Kimberlin et al., 2010; Leung et al., 2010b), preventing pattern associated molecular pattern (PAMP) recognition by RIG-I. However, evidence for end-capping interactions by mVP35 is lacking and mVP35 appears to interact with the dsRNA backbone only (Ramanan et al., 2012). The biological consequences of these differences are unclear.

Here, we compared antiviral responses to EBOV and MARV infections in THP-1 cells and investigated the mechanistic basis for the suppression of IFN-α/β responses by eVP35 and mVP35. Our data reveal that MARV infections trigger a greater IFN response than does EBOV, which correlates with a stronger inhibition of RLR signaling by eVP35 compared to mVP35. This functional difference can be mapped to VP35 IID and its capacity to block PAMP recognition by RLRs. Our data, for the first time, implicate the mode of interaction of viral VP35 with immunostimulatory RNA as a determinant of early host IFN response to filovirus infection. These observations also demonstrate that complete suppression of IFN-α/β responses is not a prerequisite for MARV to cause severe disease.