Nature Reviews Microbiology | AOP, published online 7 April 2014; doi:10.1038/nrmicro3258

VIRAL INFECTION

Marburg targets the host oxidative response

> VP24 promotes the survival of infected cells and dysregulates the host antiviral inflammatory response

Marburg virus (MARV) causes severe haemorrhagic fever in humans and non-human primates, and high viral burden and a potent and detrimental increase in cytokine production are hallmarks of infection. Two new studies now provide molecular insights into how MARV protein VP24 promotes the survival of infected cells and dysregulates the host antiviral inflammatory response, and a third study reveals the crystal structure of the protein.

VP24 from the related Ebola virus (EBOV) binds to host cell factors to inhibit interferon signalling, whereas MARV VP24 does not exhibit immunosuppressive properties and its cellular interaction partners were unknown. Using co-immunoprecipitation assays, Edwards *et al.* and Page *et al.* showed that overexpressed MARV VP24 binds to host kelch-like ECH-associated protein 1 (KEAP1), which is a negative regulator that sequesters nuclear factor erythroid 2-related factor 2 (NRF2) in the cytoplasm to prevent NRF2-dependent activation of the host antioxidant response. KEAP1 deletion mutants that lack the kelch domain — a region that contains the NRF2-binding site — lost the ability to interact with VP24, compared with the full-length protein, which suggests that the NRF2- and VP24-binding sites overlap. Consistent with this, Edwards *et al.* identified a sequence in a predicted structural loop in VP24 (termed K-loop) that resembles the KEAP1-binding motif in NRF2.

Both groups went on to assess the cellular distribution of NRF2 and found that, when co-expressed with KEAP1, NRF2 was mostly cytoplasmic, whereas overexpression of VP24 resulted in its nuclear translocation. This suggests that VP24 impairs the inhibitory interaction between NRF2 and KEAP1. In agreement with this, although Edwards *et al.* found that NRF2 and VP24 have similar binding affinities for KEAP1, both groups showed that VP24 outcompetes NRF2 for binding to KEAP1.

Furthermore, both studies reported that ectopically expressed VP24 and live MARV activate endogenous NRF2 target genes. Page *et al.* also showed that *Nrf2*$^{-/-}$ mice had higher survival rates and lower viral titres post-infection than wild-type mice. These results suggest that MARV VP24 targets the cytoprotective NRF2 pathway to increase the ability of infected cells to survive the oxidative stress that is perhaps caused by infiltrating inflammatory cells. The results also suggest that VP24-driven persistent NRF2 activation alters the usually well-controlled host inflammatory balance, which is likely to contribute to the dysregulation of the antiviral inflammatory responses and thus has a role in the pathogenesis of infection. Interestingly, EBOV VP24 did not bind to KEAP1 or increase NRF2 target gene expression; however, recombinant EBOV VP24 carrying the MARV VP24 K-loop enabled KEAP1 binding and NRF2 activation.

In a separate study, Zhang *et al.* determined the crystal structure of MARV VP24 at 2.65 Å and compared it to their previously solved structures of VP24 from two ebolaviruses, Sudan virus and Reston virus. Although these VP24 proteins share a similar core structure, there are intriguing differences; for example, the amino-terminal region of MARV VP24 is more flexible. The authors reported that residues 201–217 of MARV VP24 form an extended β-strand 'shelf' that projects from the core structure, whereas the equivalent residues of VP24 from the two ebolaviruses form shorter strands that are connected by a helical structure. Further studies are required to determine the functional significance of these structural differences.

Together, these studies provide insights into the role of VP24 in MARV pathogenesis, and the availability of the structural data should facilitate our understanding of the function of this protein in infection.

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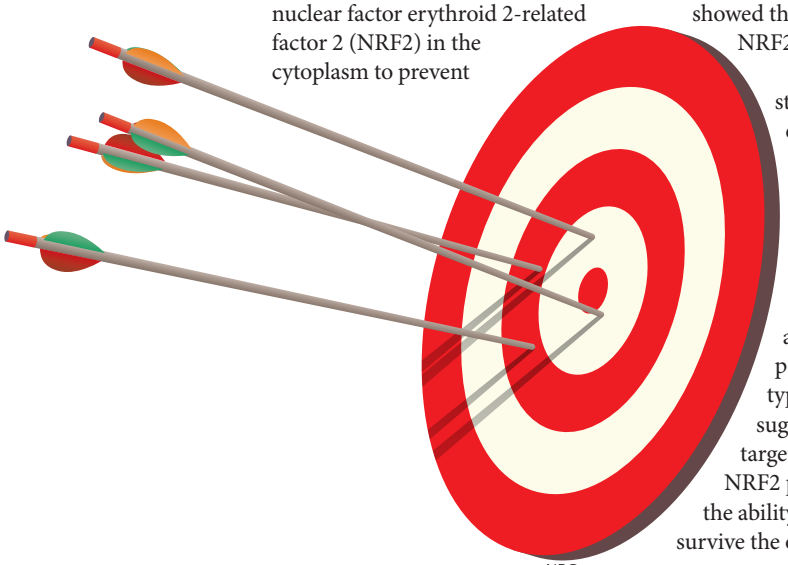

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ORIGINAL RESEARCH PAPERS Edwards, M. R. *et al.* The Marburg virus VP24 protein interacts with Keap1 to activate the cytoprotective antioxidant response pathway. *Cell Rep.* http://dx.doi.org/10.1016/j.celrep.2014.01.043 (2014) | Page, A. *et al.* Marburgvirus hijacks Nrf2-dependent pathway by targeting Nrf2-negative regulator Keap1. *Cell Rep.* http://dx.doi.org/10.1016/j.celrep.2014.02.027 (2014) | Zhang, A. P. P. *et al.* Crystal structure of Marburg virus VP24. *J. Virol.* http://dx.doi.org/10.1128/JVI.03565-13 (2014)