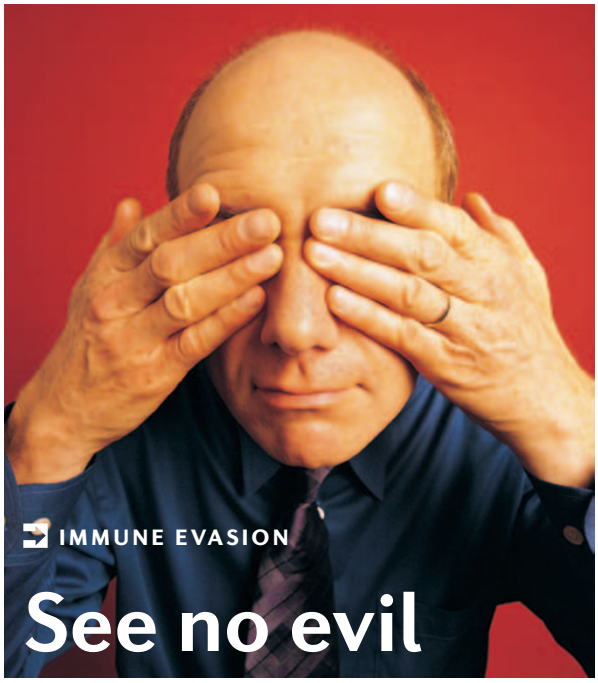
Nature Reviews Microbiology | AOP, published online 21 July 2014; corrected online 4 August 2014; doi:10.1038/nrmicro3327



Digital Vision/ Getty Images

A key contributor to the pathogenicity of measles virus is its ability to suppress host immune responses, but the molecular mechanisms that are responsible for this immune evasion are unclear. Two publications in *Cell Host & Microbe* now describe how measles virus avoids cytosolic detection by members of the retinoic acid-inducible gene I (RIG-I)-like receptor (RLR) family.

The RLR family includes RIG-I and melanoma differentiation-associated protein 5 (MDA5), which recognize viral double-stranded RNA structures. Following RNA recognition, RIG-I and MDA5 form complexes with the mitochondrial antiviral signalling protein (MAVS) via their caspase activation and recruitment domains (CARDs). These interactions trigger downstream signalling pathways that result in the production of antiviral type I interferons. RLR-induced signalling is regulated by the phosphatase PP1, which dephosphorylates specific residues in the CARDs of RIG-I and MDA5, enabling their interaction with MAVS. Notably, paramyxoviruses — the family that includes measles virus — have been shown to interfere with RLR-induced signalling pathways by targeting MDA5 via a non-structural viral protein, the V protein, although the precise mechanisms of this interaction are unknown. Now, Mesman *et al.* and Davis *et al.* show that measles virus targets PP1 to block the dephosphorylation of RIG-I and MDA5, which inhibits the production of type I interferon.

> “measles virus impairs PP1 function, which prevents the activation of RIG-I and MDA5, enabling the virus to escape cytosolic detection”

By carrying out co-immunoprecipitation (coIP) assays, Davis *et al.* found that measles virus V protein (MV-V) binds to PP1. Furthermore, the authors identified a conserved four-residue motif in the carboxy-terminal tail of MV-V that is responsible for PP1 binding. They constructed a recombinant virus strain that expressed a truncated version of MV-V lacking the C-terminal tail (VΔtail), which displayed reduced replication capacity following infection of lung epithelial cell lines, compared with wild-type virus. Analysis of VΔtail virus-infected cells at late time points following infection showed the presence of dephosphorylated MDA5. These data suggest that MV-V recruits PP1 away from MDA5, which prevents MDA5 activation by dephosphorylation.

Interestingly, at early time points following infection of primary human dendritic cells with either wild-type or VΔtail viruses, both MDA5 and RIG-I remained phosphorylated, which suggests that there is an MV-V-independent mechanism of inhibition of RLR-induced signalling. Mesman *et al.* characterized this second mechanism and, by using antibodies specific for the C-type lectin receptor DC-SIGN, found that blocking DC-SIGN decreases measles virus infection and replication. Notably, DC-SIGN triggering by measles virus prevented dephosphorylation of RIG-I and MDA5 via activation of RAF1 — a kinase that regulates signalling pathways downstream of DC-SIGN. The authors investigated a possible link between RAF1 and PP1 by analysing GADD34, which is a growth-arrest and DNA-damage protein and PP1-binding partner that had previously been implicated in the regulation of type I interferon responses. Interestingly, measles virus infection induced phosphorylation of I-1 — a known inhibitor of the activity of GADD34–PP1 complexes — in a RAF1-dependent manner, and coIP assays revealed that phosphorylated I-1 associates with PP1. Furthermore, silencing of I-1 during measles virus infection enabled RIG-I and MDA5 dephosphorylation and subsequent induction of antiviral type I interferons, which inhibited viral replication in primary dendritic cells. These data suggest that measles virus activates DC-SIGN, which triggers RAF1-mediated signalling, leading to I-1 phosphorylation and binding to GADD34–PP1 complexes, resulting in the inhibition of PP1 activity and thereby preventing an antiviral type I interferon response.

Together, these studies reveal two independent mechanisms in different cell types by which measles virus impairs PP1 function, which prevents the activation of RIG-I and MDA5, enabling the virus to escape cytosolic detection. They also highlight PP1 as a crucial component of innate immune signalling networks that is targeted by viral immune escape mechanisms.

Cláudio Nunes-Alves

ORIGINAL RESEARCH PAPERS Davis, M. E. *et al.* Antagonism of the phosphatase PP1 by the measles virus V protein is required for innate immune escape of MDA5. *Cell Host Microbe* **16**, 19–30 (2014) | Mesman, A. W. *et al.* Measles virus supresses RIG-I-like receptor activation in dendritic cells via DC-SIGN-mediated inhibition of PP1 phosphatases. *Cell Host Microbe* **16**, 31–42 (2014)

In the original version of this highlight, retinoic-acid-inducible gene I (RIG-I) was incorrectly defined as retinoic acid-inducible protein 1 (RIG1). The online version of this article has been corrected. We apologize for any confusion caused.