INNATE IMMUNITY

Sensing viruses

Recently there have been marked advances in determining the mechanisms by which innate immune cells respond to intracellular pathogens. The use of *in vitro* studies has resulted in the identification of mitochondrial antiviral signalling protein (MAVS; also known as IPS1, CARDIF and VISA) as an important adaptor protein that can link intracellular pathogen recognition with activation of the transcription factors nuclear factor-κB (NF-κB) and interferon-regulatory factor 3 (IRF3). New research shows a specific and essential role for MAVS *in vivo* in the innate immune response to viruses.

To elucidate the role of MAVS *in vivo*, Sun *et al.* generated *Mavs*$^{-/-}$ mice by homologous recombination. *Mavs*$^{-/-}$ and *Mavs*$^{+/-}$ mice infected with vesicular stomatitis virus (VSV) (an RNA virus) died within 4 days of infection, whereas most wild-type mice survived. This indicates an important role for MAVS in protection against VSV-induced mortality. In addition, mouse embryonic fibroblasts (MEFs) from *Mavs*$^{-/-}$ mice were more permissive to VSV replication compared with MEFs from wild-type mice.

Infection of MEFs, macrophages and conventional dendritic cells from *Mavs*$^{-/-}$ mice with Sendai virus (SEV) (an RNA virus) did not activate either NF-κB or IRF3, or induce type I interferons (IFNs). However, induction of type I IFNs was intact in *Mavs*$^{-/-}$ mice in response to Toll-like receptor (TLR) ligands, such as lipopolysaccharide and the synthetic double-stranded RNA analogue poly I:C (polyinosinic–polycytidylic acid). Because activation of NF-κB and IRF3 by viruses involves at least two signalling pathways — the TLR-signalling pathway and a pathway that uses cytoplasmic receptors, such as retinoic-acid-inducible gene I (RIG-I) and melanoma-differentiation-associated gene 5 (MDA5) — these data indicate that MAVS is required for antiviral immunity but not for TLR-induced immune responses.

Interestingly, induction of type I IFNs by transfection of MEFs with poly I:C, which introduces the RNA analogue into the cytosol, was dependent on MAVS. In addition, MAVS is required for type I IFN induction by poly I:C *in vivo.* A recent study has shown that IFNβ production induced by SEV and VSV requires RIG-I, whereas transfected poly I:C induces IFNβ production through MDA5. Therefore, it would seem that MAVS functions downstream of both of these receptors and might function as a convergence point for these signalling pathways.

Recent studies have also indicated that MAVS might be involved in the induction of type I IFNs in response to cytosolic B-form DNA and *Listeria monocytogenes.* However, induction of type I IFNs by macrophages transfected with B-form DNA or infected with *L. monocytogenes* was similar in *Mavs*$^{-/-}$ mice and wild-type mice. Similarly, a recent study published in *FEBS Letters* also showed, using siRNA (small interfering RNA)-mediated knockdown of *Mavs*, that loss of MAVS did not affect induction of type I IFNs by *L. monocytogenes.*

Therefore, MAVS is not an adaptor protein for all cytoplasmic pathogen sensors, but does have a specific and essential role in antiviral immunity independent of TLR signalling.

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ORIGINAL RESEARCH PAPERS Sun, Q. *et al.* The specific and essential role of MAVS in antiviral innate immune responses. *Immunity* **24**, 633–642 (2006) | Soulat, D. *et al.* Cytoplasmic *Listeria monocytogenes* stimulates IFN-β synthesis without requiring the adapter protein MAVS. *FEBS Lett.* **580**, 2341–2346 (2006)