INNATE IMMUNITY

Detailed detection

Two recent papers have revealed further details of how RNA viruses such as West Nile virus (WNV) and influenza virus engage the host innate immune system.

Recognition of RNA virus infection by pattern recognition receptors (PRRs) triggers an antiviral signalling cascade that culminates in the induction of type I interferons (IFNs) and a proinflammatory response. Earlier work had established that the PRRs that are involved in the recognition of WNV are RIG-I (retinoic acid-inducible gene I protein) and MDA5 (melanoma differentiation-associated protein 5). These RIG-I-like receptors (RLRs) function cooperatively in the recognition of WNV through the downstream mitochondria-associated RLR adaptor protein IPS1 (IFN-β promoter stimulator 1; also known as MAVS).

Suthar and colleagues present a detailed analysis of the innate and adaptive immune responses to WNV infection. Analysis of the effects of WNV challenge on wild-type and *Ips1*$^{-/-}$ mice confirmed that IPS1 is essential for the control of WNV replication, as mice lacking IPS1 were highly susceptible to WNV infection and showed increased viraemia compared with wild-type mice. Progression of the infection was followed, and the authors found that IPS1 is involved in restricting the tissue tropism of WNV and in the entry of this neurotropic virus into the central nervous system. At the cellular level, examination of dendritic cells, macrophages and primary cortical neurons harvested from IPS1-knockout mice showed that in the absence of IPS1 there was increased WNV replication and a decreased IFN response.

Suthar *et al.* went on to look at the overall inflammatory response to WNV infection and found that in the absence of IPS1 the levels of proinflammatory chemokines and cytokines in the sera were higher than levels in wild-type mice and that this was accompanied by an elevated cellular inflammatory response, indicating that IPS1-dependent and IPS1-independent pathways are involved. In addition, analysis of the humoral immune response in *Ips1*$^{-/-}$ mice showed that the immunoglobulin (Ig) profiles were altered, with sera from *Ips1*$^{-/-}$ mice displaying higher WNV-specific IgM and IgG antibody titres but having poorer neutralization capacities than sera from wild-type mice. Moreover, the numbers of circulating regulatory T cells, which can depress the inflammatory response, were decreased in the absence of IPS1. Taken together, these data indicate that IPS1 has a central role in controlling the innate immune response to WNV infection and couples this with regulation of the adaptive response.

Another recent study on the response to RNA viruses focused further upstream on the long-standing question of the precise nature of the viral nucleic-acid motif that is recognized by RLRs. Until now, the RNA ligands that are recognised by RLRs have mainly been studied using synthetic analogues, and at least six RIG-I ligands have been identified. In a recent issue of *Cell*, Jan Rehwinkel, Choon Ping Tan and colleagues report that the main physiological RIG-I agonist in cells infected with the negative-sense single-stranded RNA viruses influenza A virus and Sendai virus is single-stranded viral genomic RNA carrying a 5′-triphosphate and not viral transcripts, replication intermediates or RNase L cleavage products.

Together, these studies help to further define the mechanistic nature of the host response to RNA virus infection.

Sheilagh Molloy

> “IPS1 has a central role in controlling the innate immune response to WNV infection and … regulation of the adaptive response.”

ORIGINAL RESEARCH PAPERS Suthar, M. S. *et al.* IPS-1 is essential for the control of West Nile virus infection and immunity. *PLoS Pathog.* e1000757 (2010) | Rehwinkel, J. *et al.* RIG-I detects viral genomic RNA during negative-strand RNA virus infection. *Cell* **140**, 397–408 (2010)