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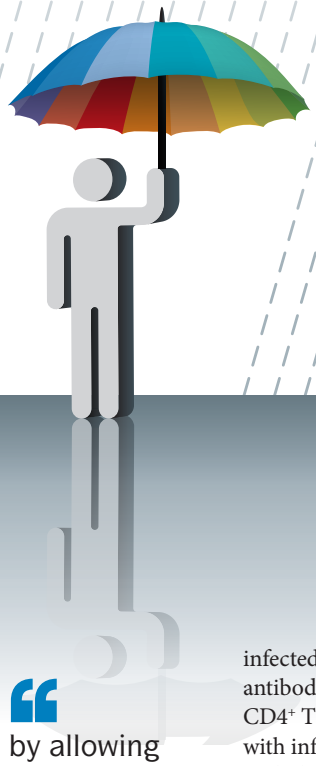

VIRAL IMMUNITY

Shelter from interferons

New research has revealed a mechanism that explains how the innate immune system inhibits viral propagation but still allows the production of enough viral antigens to stimulate an effective adaptive immune response. The answer lies in a subset of macrophages that resists the antiviral effects of type I interferons (IFNs).

Soon after systemic infection, viruses are captured by phagocytic innate immune cells, which suppress viral propagation through the production of type I IFNs. Indeed, in the case of mouse vesicular stomatitis virus (VSV), the authors showed that macrophages in the red pulp of the spleen and Kupffer cells in the liver effectively capture the virus and inhibit its replication in a type I IFN-dependent manner. However, 7 hours after infection, replicating virus could be detected in CD169$^+$ macrophages in the marginal zone of the spleen but not elsewhere.

Further analysis of the marginal zone CD169$^+$ macrophages showed that they express higher levels of ubiquitin-specific peptidase 18 (USP18) — which is known to inhibit type I IFN signalling — than F4/80$^+$ macrophages from the red pulp. USP18 overexpression was found to be responsible for allowing VSV replication, as low amounts of viral proteins were detectable in CD169$^+$ macrophages from *Usp18*$^{-/-}$ mice.

Given that ultraviolet light-inactivated, replication-deficient VSV generated poor antiviral B and T cell responses, the authors investigated the involvement of CD169$^+$ macrophages in the generation of adaptive immune responses to VSV. Mice that were specifically depleted of CD169$^+$ macrophages showed delayed and diminished B cell responses to VSV relative to control mice. Moreover, *Usp18*$^{-/-}$ mice infected with VSV had delayed antibody responses and reduced CD4$^+$ T cell responses compared with infected wild-type mice. No such differences were observed if the mice were infected with replication-deficient VSV, confirming that VSV replication in CD169$^+$ macrophages was responsible for the induction of adaptive immune responses. Failure to generate strong adaptive immune responses led to the spread of the virus and death of the mice. So, by allowing viral replication in the presence of type I IFNs, marginal zone macrophages ensure the production of sufficient antigens for the activation of protective adaptive immune responses.

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Lucy Bird

ORIGINAL RESEARCH PAPER Honke, N. *et al.* Enforced viral replication activates adaptive immunity and is essential for the control of a cytopathic virus. *Nature Immunol.* 20 Nov 2011 (doi:10.1038/ni.2169)