ANTIVIRAL IMMUNITY

Re-routing the interferon response through B cells

> …a new route to IFNα/β production in response to mouse cytomegalovirus (MCMV) … involves B cells and is dependent on lymphotoxin (LT).

Immunologists typically think of the innate interferon-α/β (IFNα/β) response to viruses as being mediated by plasmacytoid dendritic cells in a Toll-like receptor (TLR)-dependent manner. Now, Kirsten Schneider, Carl Ware, Chris Benedict and colleagues describe a new route to IFNα/β production in response to mouse cytomegalovirus (MCMV) that involves B cells and is dependent on lymphotoxin (LT).

The IFNα/β response to MCMV infection in the spleen of C57BL/6 and BALB/c mice was shown to be biphasic, with a peak at 8 hours after infection followed by a second more sustained accumulation of IFNα/β between 36 and 72 hours after infection. Mice deficient for both ligands of the LTβ receptor (*Ltb*$^{-/-}$*Light*$^{-/-}$ mice) had a decrease in the level of mRNA encoding IFNβ in the spleen during the first peak of the IFNα/β response to MCMV, but not by 48 hours after infection. The defective first phase of the IFNα/β response to infection could be partially restored using an agonistic LTβR-specific antibody. By contrast, mice deficient for both MyD88 and TRIF, which lack TLR signalling, had no defect in the early-phase IFNα/β response to MCMV. So, the initial IFNα/β response to MCMV in the spleen is LTβR dependent but TLR independent.

The authors then carried out bone-marrow chimaera experiments to determine whether LTβR expression by haematopoietic cells or radio-resistant stromal cells is required for IFNα/β production in the spleen. LTβR-deficient mice reconstituted with wild-type bone marrow, but not wild-type mice reconstituted with LTβR-deficient bone marrow, had a defective early-phase IFNα/β response. This indicates that stromal-cell expression of LTβR is required to mount the initial IFNα/β response to MCMV. Activation of the nuclear factor-κB (NF-κB) pathway by LTβR requires NF-κB-inducing kinase (NIK); *aly/aly* mice (which have a functional mutation in NIK) infected with MCMV had a marked decrease in IFNα/β production at 8 hours after infection. So, NF-κB signalling induced through LTβR in stromal cells is required for the early IFNα/β response to MCMV.

Naive B cells and CD4^{+} T cells in the spleen constitutively express LTβ on their surface and are therefore potential sources of the LTβR ligand required for IFNα/β induction. Mice that were deficient in B cells and, more specifically, mice that were conditionally deficient in LTβ in B cells (but not mice that were deficient in LTβ in T cells) had a defective early-phase IFNα/β response to MCMV, which links naive B cells to innate immunity through the LTβ–LTβR pathway.

The authors speculate that if dysregulated during persistent infection, this pathway might contribute to autoimmune diseases such as systemic lupus erythematosus, in which both B cells and IFNα/β are known to have a role in pathogenesis.

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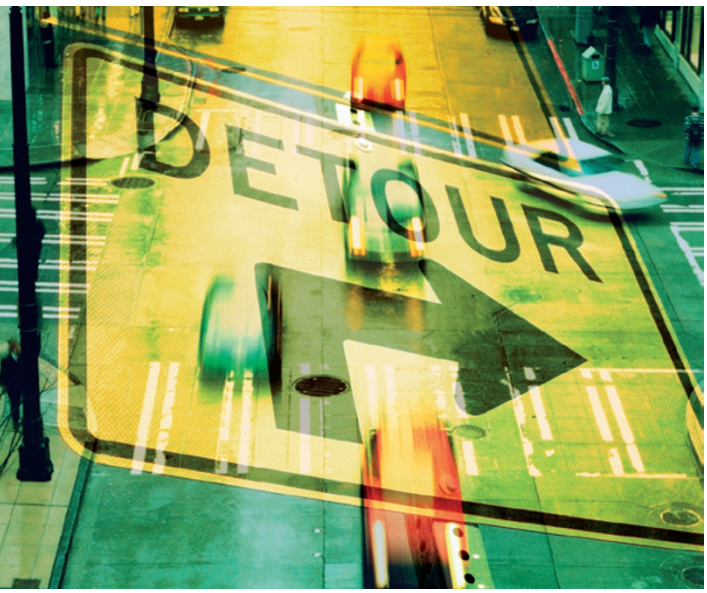

IMAGE SOURCE

ORIGINAL RESEARCH PAPER Schneider, K. *et al.* Lymphotoxin-mediated crosstalk between B cells and splenic stroma promotes the initial type I interferon response to cytomegalovirus. *Cell Host Microbe* **3**, 67–76 (2008)