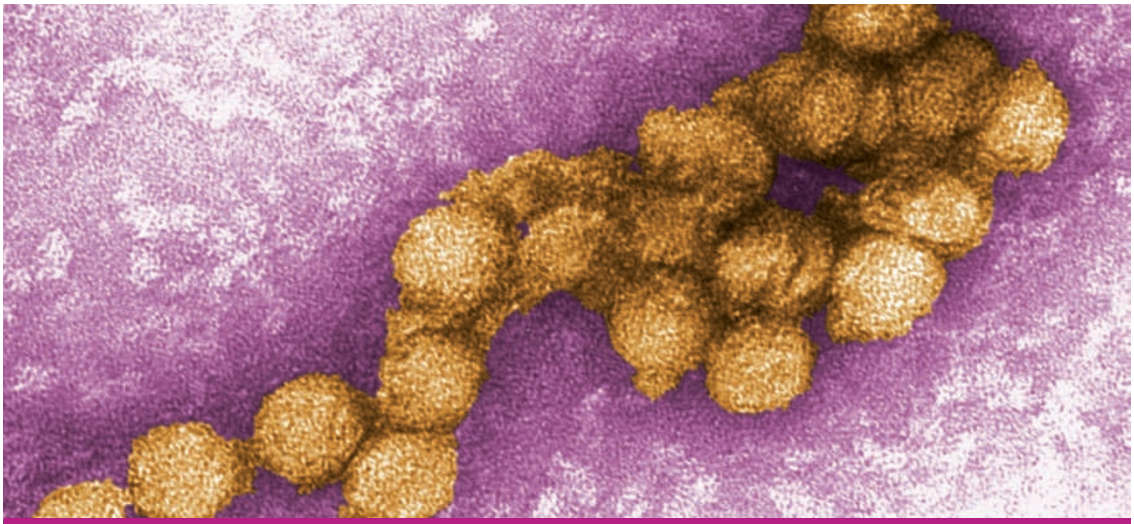

West Nile virus virons pseudocoloured brown. Image sourced from CDC/P.E. Rollin

INNATE IMMUNITY

Not-so-lucky 7 for West Nile virus

Infection with West Nile virus can have a range of outcomes, from asymptomatic infection to deadly encephalitis, for which there is currently no treatment. Town and colleagues report in a recent issue of *Immunity* that Toll-like receptor 7 (TLR7) and interleukin-23 (IL-23) are important mediators of a successful host response.

West Nile virus is a single-stranded (ssRNA) RNA virus that enters the host through a mosquito bite and can infect most tissues, including the brain. Host responses to viral infections often involve TLRs; these proteins sense molecules derived from pathogens and then transduce a signal, in most cases through MyD88, to elicit an immune response. Because TLR7 can recognize ssRNA and is known to play a part in the defence against other viral pathogens, Town and colleagues tested whether TLR7 had a role in the response to West Nile infection. They found that TLR7-deficient and MyD88-deficient mice were more susceptible to West Nile virus infection; deletion of the gene encoding TLR9, which had been shown to sense viral DNA, had no effect on the outcome of the infection. Viral load was significantly higher in the mutant mice, particularly in the brain and liver. Serum levels of several innate immune cytokines were increased in the absence of TLR7, but curiously, the levels of IL-12β (also known as IL-12 subunit p40; shared by full-length IL-12 and IL-23) and IL-23 were lower in mutant mice. The authors noticed that in infected wild-type brains and livers, leukocytes and macrophages were in close proximity to infected neurons, sometimes even overlapping, but did not detect this apposition in TLR7-deficient or MyD88-deficient mice, even though such mice had a higher virus burden. Peritoneal injection of the mutant mice with thioglycollate, which induces macrophage migration, showed that mutant mouse macrophages could still respond to a chemotaxic signal.

In an *in vitro* motility assay, wild-type macrophages, but not TLR7-deficient macrophages, were attracted by supernatants of neurons infected with West Nile virus, a TLR7 agonist and IL-23, although TLR7-deficient macrophages could still move towards the positive control, C-C motif chemokine 2 (CCL2; also known as MCP1). To elucidate the role of IL-23 *in vivo*, the authors infected IL-23-deficient and MyD88-deficient mice with West Nile virus, and found that fewer macrophages infiltrated the infected areas of the brain than in IL-12-deficient or wild-type mice. In agreement with a role for IL-23 in protection, IL-23-deficient and MyD88-deficient mice were also more susceptible to viral infection and less likely to survive a lethal challenge with West Nile virus.

On the basis of these experiments, the authors suggest that brain-resident macrophages (called microglia) detect West Nile virus ssRNA through TLR7 and signal through MyD88, leading to secretion of high levels of IL-23. This attracts infiltrating macrophages and other leukocytes, which neutralize and clear the infection. If this pathway could be exploited therapeutically, it could form the basis for a novel treatment of West Nile virus.

Christiaan van Ooij

> “...IL-23-deficient and MyD88-deficient mice were also more susceptible to viral infection...”

ORIGINAL RESEARCH PAPER Town, T. *et al.* Toll-like receptor 7 mitigates lethal West Nile encephalitis via interleukin 23-dependent immune cell infiltration and homing. *Immunity* **30**, 242–253 (2009)