

 VIRAL PATHOGENESIS

## Turning virus spread on its head

Understanding how viruses spread from the initial site of infection to become systemic and cause symptoms in a host is an important aspect of viral pathogenesis. Reporting in *Cell Host & Microbe*, Sacher *et al.* reveal that although murine cytomegalovirus (MCMV) replicates to high titres in the liver, none of the hepatocyte-derived viruses spread to other tissues. Surprisingly, only endothelial-cell-derived viruses contribute to the systemic spread of MCMV.

In the classic model of systemic viral infection, primary viraemia spreads viruses from the infection site to organs. Following replication in organs, such as the liver or spleen, secondary viraemia spreads viruses throughout the host. Sacher *et al.* exploited the Cre-recombinase system to pinpoint which host cell types produce viruses that spread during systemic infection with MCMV. They constructed recombinant MCMV that can only express the fluorescent reporter gene *egfp* (enhanced green fluorescent protein), which is under the control of the major immediate early promoter of MCMV, if a stop codon has been excised by the Cre recombinase. The key feature of these

experiments is that infecting viruses and disseminated viruses can be distinguished by fluorescence.

Transgenic mice that express the Cre recombinase in different cell types were used as hosts for infection with EGFP-tagged MCMV. Endothelial cells and hepatocytes were both infected productively by MCMV after inoculation and primary viraemia. However, secondary viraemia was almost exclusively due to virus that was produced in endothelial cells. Not only did hepatocyte-derived viruses fail to spread in the blood of normal mice, they also failed to spread in immunosuppressed mice. Intriguingly, although 70% of the total MCMV load in a mouse is present in the liver, this virus is not disseminated to other target organs. Understanding why viruses replicate in the liver, but do not spread, will be the next step in this research.

Using novel techniques has revolutionized our understanding of fundamental aspects of MCMV pathogenesis, and these techniques could now be applied to other DNA viruses.



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**ORIGINAL RESEARCH PAPER** Sacher, T. *et al.*  
The major virus-producing cell type during murine cytomegalovirus infection, the hepatocyte, is not the source of virus dissemination in the host. *Cell Host Microbe* **3**, 263–272 (2008)