URLs

Virology

Fatal alliance

Murine cytomegalovirus (MCMV) strains can benefit from each other by coinfecting cells, according to a paper published in the *Journal of Virology*.

Human cytomegalovirus (HCMV) is a ubiquitous human herpesvirus that causes severe and fatal disease in immunocompromised individuals. As primary HCMV infection does not fully protect against reinfection, multiple strains can persist in a host over a lifetime. The MCMV infection model is currently the most intensively studied *in vivo* model of CMV infection. To evaluate the interactions between MCMV variants, Čičin-Šain *et al.* infected mice with wild-type (WT) MCMV and/or attenuated MCMV variants of which the *M36* gene is disrupted by a green fluorescent protein (GFP) expression cassette (Tn-M36.A MCMV) or replaced by a kanamycin-resistance gene (Δ M36-MCMV).

Whereas inoculation of just Tn-M36.A MCMV alone led to no MCMV detection in the lung, inoculation of mice with both WT-MCMV and Tn-M36.A MCMV led to the detection of GFP-expressing virus in the lungs of all mice. Also, studying the *in vivo* growth kinetics of MCMV in spleen, lungs and salivary glands, WT-MCMV was found to support not only the growth but also the dissemination of Δ M36-MCMV. This helper effect of WT-MCMV was based primarily on *trans*-complementation. Functional complementation was found to occur not only

between WT and attenuated virus, but also between two fully replication-competent viruses.

Using a reporter system in which GFP expression requires functional complementation between two viruses, Čičin-Šain and co-workers found that expression of GFP required coinfection of cells. Direct evidence for simultaneous replication of two viruses in the same cell was provided by two-colour *in situ* hybridization of serial tissue sections. Upon inoculation of immunocompromised mice with red-tagged WT-MCMV and black-tagged Δ M36-MCMV, intranuclear inclusion bodies (which result from the accumulation of viral DNA packages into nucleocapsids) containing both viruses were detected in the liver, at frequencies higher than statistically predicted. However, this was only found to occur if both viruses were

administered to the same footpad, indicating that WT-MCMV and Δ M36-MCMV have to meet at the site of infection and comigrate during their dissemination. Once in the liver, they replicate both jointly and independently.

These results might explain the increased virus load in, and poor clinical prognosis of, immunocompromised individuals infected with multiple CMV variants, as otherwise moderately pathogenic strains might increase their virus fitness through *trans*-complementation in coinfecting cells.

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References and links

ORIGINAL RESEARCH PAPER Čičin-Šain, L., Podlech, J., Messerle, M., Reddehase M. J. & Koszinowski, U. H. Frequent coinfection of cells explains functional *in vivo* complementation between cytomegalovirus variants in the multiply infected host. *J. Virol.* **79**, 9492–9502 (2005)