

# RESEARCH HIGHLIGHTS

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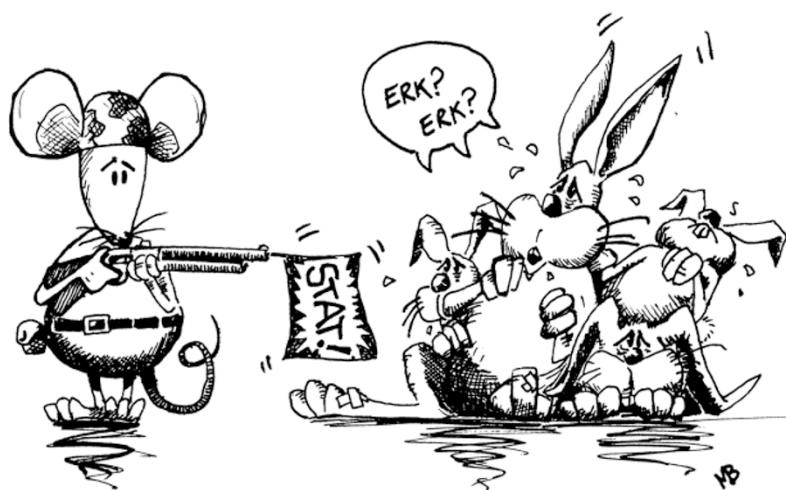
## VIROLOGY

# Of mice and myxoma

Myxomatosis, a lethal disease of rabbits, is caused by the myxoma virus — a member of the poxvirus family. The myxoma virus does not cause disease in any other vertebrate species, but the molecular basis of this strict species restriction — a characteristic of all poxviruses — is still unclear. Now, reporting in *Nature Immunology*, Grant McFadden and colleagues show that the myxoma virus species barrier is mediated by a host-cell signalling cascade — the extracellular signal-regulated kinase (Erk) 1/2–interferon–STAT1 signalling pathway.

Although myxomatosis only affects rabbits, the myxoma virus can infect mouse cells *in vitro*, providing scientists with model systems to study poxvirus host restriction. So, McFadden and co-workers infected primary mouse embryonic fibroblasts (pMEFs) with myxoma virus that expressed  $\beta$ -galactosidase under the control of a late viral gene promoter. X-gal assays of infected cells showed that the virus had successfully entered the pMEFs, but that the infection had aborted coincident with late viral gene expression — a stage at which the virus interacts with cell signalling pathways.

So, it seems that host-cell signalling cascades might restrict myxoma virus replication and, sure enough, the infection of pMEFs with myxoma virus in the presence of U0126 — an inhibitor of the signalling molecule Erk1/2 — resulted



in permissive viral replication. Activated Erk1/2 usually translocates to the nucleus, where it phosphorylates Elk1. Surprisingly, in myxoma-virus-infected pMEFs, Elk1 remained unphosphorylated, and phosphorylated Erk1/2 was retained in the cytoplasm. The authors reasoned that, in myxoma-virus-infected cells, Erk1/2 might mediate its potent antiviral effect by interacting with other cytoplasmic signalling molecules such as interferon regulatory factor 3 (IRF3) — an important component of the type 1 interferon pathway.

A diverse set of experiments showed that this was indeed the case. Myxoma-virus infection of pMEFs was associated with increased levels of type 1 interferon mRNA, which were substantially reduced on inhibition of Erk1/2. Also, the phosphorylation of STAT1, a downstream mediator of interferon 1, was dependent on Erk1/2 activity, and an association between Erk1/2 and IRF3 was revealed — IRF3 was not phosphorylated and was retained in the cytoplasm of

myxoma-virus-infected cells on inhibition of Erk1/2.

These *in vitro* results were complemented by an *in vivo* demonstration of cross-species infection. *Stat1*<sup>-/-</sup> mice were infected with intracranial myxoma and, in contrast to wild-type mice, which are resistant to this rabbit-specific virus, the *Stat1*<sup>-/-</sup> mice rapidly succumbed to infection.

As many viruses exploit the Erk1/2 pathway to promote their replication, these studies reveal the complexities of virus–host interactions and show that modulation of the same host-cell signalling pathway by different viruses can have profound effects on the outcome of infection. And immunologists will also be taking note as these studies have shown a “previously unrecognized link between Erk1/2 signalling and type 1 interferon induction”.

Shannon Amoils

## References and links

**ORIGINAL RESEARCH PAPER** Wang, F. *et al.* Disruption of Erk-dependent type I interferon induction breaks the myxoma virus species barrier. *Nature Immunol.* **5**, 1266–1274 (2004)

## WEB SITE

Grant McFadden's laboratory: <http://www.robots.ca/biotherapeutics/McFadden.htm>