IN THE NEWS

Foot-and-mouth vaccine
Emergency ring vaccination should be used as a 'tool of first resort' to contain future outbreaks of foot-and-mouth disease, according to a report released by the Royal Society (*BBC News*). The report is the result of an inquiry commissioned by the UK government to investigate the scientific aspects of transmission, prevention and control of infectious disease in animals.

Last year, almost 6 million animals were slaughtered (*New Scientist*) as the result of a 'contiguous cull' policy that aimed to halt the development of the foot-and-mouth epidemic, which cost the UK almost £8 billion. Although the Royal Society report acknowledges the importance of culling, movement control and rapid diagnosis, it states that, "in many cases, this will not be sufficient to guarantee that the outbreak does not develop into an epidemic" (*BBC News*). Last year, farmers were reluctant to support vaccination because of concerns over vaccine efficacy and that it might lead to a lengthy ban on meat exports. Since last year, the international rules governing the export of meat from vaccinated animals have been relaxed. According to Sir Brian Follett, who chaired the investigating committee, "we believe in most situations we should employ vaccination and not mass culling" (*Reuters*). The report also encourages scientists to develop a vaccine that would induce sterile immunity against different foot-and-mouth disease virus strains.

Meanwhile, Bobby Waugh, the Northumberland farmer at the centre of last year's outbreak, has been found guilty of failing to alert officials that his pigs had the disease (*Guardian Unlimited*). He has been fined and banned from keeping farm animals for 15 years.

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NATURAL KILLER CELLS

A fine balance

The function of natural killer (NK) cells is controlled by the balance between signals that are received from inhibitory and activating receptors. *Ly49* genes in rodents encode both types of receptor; the main difference is that inhibitory receptors have cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIMs), whereas immunoreceptor tyrosine-based activation motifs (ITAMs) are found in the adaptor molecules — such as DAP12 — that associate with activating receptors. Although the extracellular domains of activating and inhibitory receptors are highly homologous, it is generally believed that they bind different ligands. Whereas inhibitory receptors bind MHC class I ligands, this does not seem to be the case for activating receptors, the ligands of which are largely uncharacterized. Now, two studies have shown that Ly49H, an activating receptor, can bind m157, an MHC-like molecule that is encoded by murine cytomegalovirus (MCMV).

Recent studies have shown that the expression of Ly49H is protective against infection with MCMV in resistant mice, but the mechanism of protection was unclear. To investigate this, Arase *et al.* developed reporter cells that were transfected with a nuclear factor of activated T cells (NFAT)–GFP reporter construct and the Ly49H protein, as well as the DAP12 adaptor molecule, which is essential for the activating function of Ly49H. When these cells were co-cultured with MCMV-infected cells, they turned green, which indicates the presence of a ligand for Ly49H on the infected cells. The Ly49H$^+$ reporter cells could recognize MCMV-infected cells from β_2-microglobulin-deficient and transporter for antigen processing (TAP)-deficient mice, which indicates that the ligand is unlikely to be a viral peptide presented by an MHC class I molecule. The viral ligand was identified as m157 using a panel of deletion mutants in this system.

Smith *et al.* used a similar approach to identify m157. They analysed the genome of MCMV, looking for open reading frames (ORFs) that have potential MHC folds, and they identified 12 such ORFs. Complementary DNAs were generated and transfected into cells, and the cells were assessed for their ability to interact with Ly49H$^+$ NK cells. Only transfectants that expressed m157 were able to do so. It will be interesting to investigate the roles of the other 11 viral MHC-like molecules that were discovered.

However, it doesn't make much sense that MCMV expresses a viral protein that interacts with an activating NK-cell receptor to stimulate innate immune reactions. How does the virus benefit from retaining expression of m157? Smith *et al.* suggest that m157 might interfere with the host response by affecting the assembly and maturation of MHC class I molecules. Although this has not been discounted yet, an alternative possibility, suggested by both groups, is that Ly49H might also be able to interact with an inhibitory receptor, and that it is this interaction that is important for conferring host susceptibility in particular strains of mice. This was indeed found to be the case. Arase *et al.* suggest that 129/J mice are susceptible to MCMV infection because m157 is able to interact with Ly49I, an inhibitory receptor, which could provide a selective advantage to the virus by dampening immune responses. Arase *et al.* also speculate that activating NK-cell receptors could have evolved under pathogen-driven selective pressure.

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References and links

ORIGINAL RESEARCH PAPER Arase, H., Mocarski, E. S., Campbell, A. E., Hill, A. B. & Lanier, L. L. Direct recognition of cytomegalovirus by activating and inhibitory NK cell receptors. *Science* **296**, 1323–1326 (2002) | Smith, H. R. C. *et al.* Recognition of a virus-encoded ligand by a natural killer cell activation receptor. *Proc. Natl Acad. Sci. USA* **99**, 8826–8831 (2002)
FURTHER READING Cerwenka, A. & Lanier, L. L. Natural killer cells, viruses and cancer. *Nature Rev. Immunol.* **1**, 41–49 (2002)