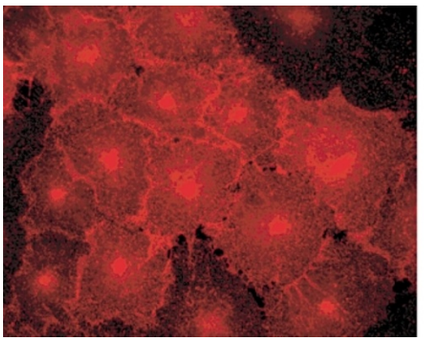
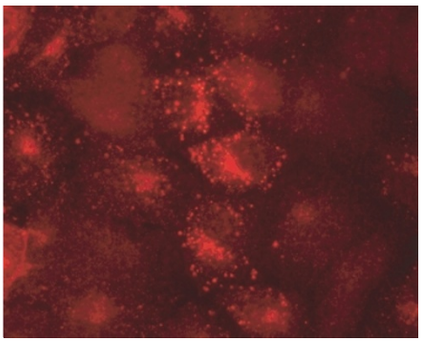
VIRAL IMMUNITY

Squatters' rights!



Uninfected



Wild-type adenovirus

An indirect immunofluorescence image using a mouse monoclonal antibody specific for TRAIL receptor 1. Courtesy of Ann Tollefson, St Louis University, USA.

As any housing officer will tell you, squatters (people who take unauthorized possession of unoccupied premises) use many tricks to avoid detection and eviction. Viruses use similarly cunning mechanisms to ensure that the cells they reside in are not targeted for destruction, via apoptosis, by the immune system. Tumour-necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), a member of the TNF superfamily, is emerging as an important molecule used by cells of the immune system to kill virus-infected cells, but how, or if, viruses can inhibit TRAIL-induced apoptosis is unknown. Tollefson and colleagues now report, in the *Journal of Virology*, that adenoviruses have evolved proteins that inhibit TRAIL-induced apoptosis, so enabling persistance of the viral infection.

Previous studies have established that proteins encoded by the E1B and E3 transcription units of adenovirus, including E1B-19K, E3-14.7K and the E3 protein RID (receptor internalization and degradation), protect infected cells from apoptosis induced by TNF-α and Fas ligand (FasL). In the present study, the authors carried out apoptosis assays on A549 human lung carcinoma cells infected with wild-type adenovirus or with mutants that lack one or more E3 or E1B protein in the presence of TRAIL and cycloheximide (which increases the sensitivity of cells to TRAIL-induced apoptosis). Mock-infected cells underwent apoptosis, as did cells infected with mutants that lacked the expression of RID, E3-14.7K and E1B-19K. However, cells infected with wild-type adenovirus or mutants expressing RID, but not E1B-19K or E3-14.7K, remained viable. Therefore, the adenoviral protein RID can block TRAIL-induced apoptosis.

How does RID inhibit the TRAIL pathway? The authors have previously shown that RID proteins protect against Fas-induced apoptosis by causing internalization and degradation of cell-surface Fas. Here, they show that the same applies for TRAIL; TRAIL-receptor 1 is cleared from the surface of cells infected by wild-type adenovirus, or any mutant expressing RID, and is transported to lysosomes for degradation. This study therefore provides an insight into how adenoviruses inactivate TRAIL-induced apoptotic pathways and so avoid eviction.

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Tollefson, A. E. *et al*. Inhibition of TRAIL-induced apoptosis and forced internalization of TRAIL receptor 1 by adenovirus proteins. *J. Virol.* **75**, 8875–8887 (2001)

FURTHER READING Tollefson, A. E. *et al*. Forced degradation of Fas inhibits apoptosis in adenovirus-infected cells. *Nature* **392**, 726–730 (1998)

MUCOSAL IMMUNITY

Defensive position

The body's mucosal surfaces are defended by a coating of immunoglobulin A. In the gut, IgA is secreted by antibody-forming cells (AFCs) that are positioned in a crucial immune-effector site — the villus lamina propria (LP). These IgA$^+$ AFCs were thought to originate in germinal centres within descrete inductive immune sites known as Peyer's patches (PP). But a recent report in *Nature* from Tasuku Honjo's group shows that this is not the whole story.

An initial clue that the origins of IgA$^+$ AFCs might be different came from studies of mice deficient in activation-induced cytidine deaminase (*AID*). B cells from *AID*$^{-/-}$ mice cannot switch their immunoglobulin class, and there is a striking accumulation of IgM$^+$ B cells and AFCs in the gut LP. This led the authors to propose that the LP IgM$^+$ B cells might be the precursors of both IgM$^+$ LP AFCs in *AID*$^{-/-}$ mice and IgA$^+$ AFCs in wild-type mice.

If LP IgA$^+$ AFCs are generated *in situ*, then actively switching B cells should be present in the LP. But how can this transient event be detected? The authors used three molecular indicators: AID, which is expressed only in B cells undergoing class switching; germ-line transcripts of the α-chain gene, which are produced just prior to switching; and circular transcripts, which are short-lived by-products of class-switch recombination. These indicators show that both LP and PP IgA$^+$ B cells have recently class-switched.

***In vitro* and *in vivo* experiments showed that LP IgM$^+$ B cells have a greater tendancy than PP IgM$^+$ B cells to differentiate into IgA$^+$ AFCs. But what is it about the micorenvironment of the LP that supports switching from IgM to IgA, an event previously thought to be restricted to germinal centres? The authors show that stromal cells isolated from the LP enhance the switching of splenic B cells to IgA, and suggest that factors secreted by the stromal cells, particularly transforming growth factor-β, might promote differentiation to IgA$^+$ AFCs.**

This study indicates that, in addition to being a crucial effector site, the gut LP is an important inductive site of the gut mucosal immune system.

Jen Bell

References and links

ORIGINAL RESEARCH PAPER Fagarasan, S., Kinoshita, K., Muramatsu, M., Ikuta, K. & Honjo, T. *In situ* class switching and differentiation to IgA-producing cells in the gut lamina propria. *Nature* **413**, 639–644 (2001)

FURTHER READING Nagler-Anderson, C.A. Man the barrier! Strategic defences in the intestinal mucosa. *Nature Rev. Immunol.* **1**, 59–67 (2001)

WEB SITE Taksuku Honjo's lab: http://www2.mfour.med.kyoto-u.ac.jp