VIRAL PATHOGENESIS

Live and let live

Links

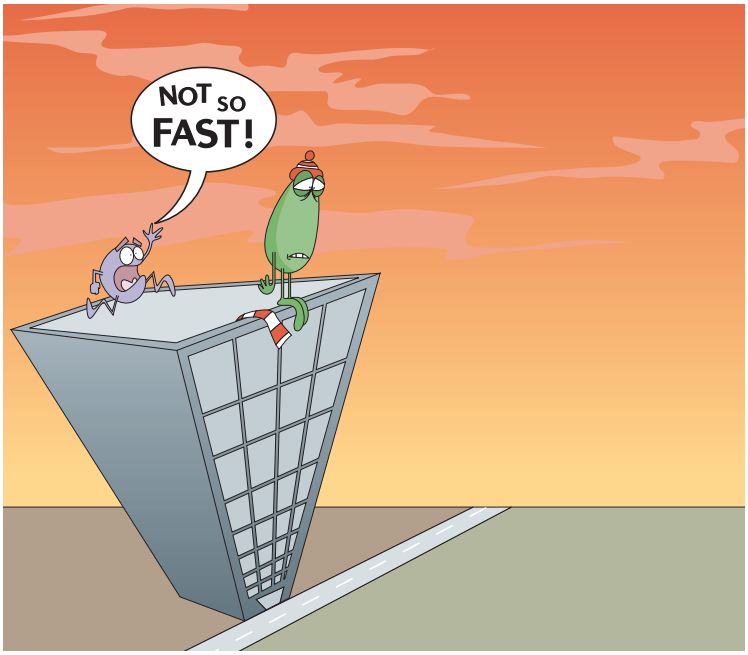
EBV
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genome&cmd=Retrieve&dopt=Overview&list_uids=19000

BHRF1
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=3783706

BALF1
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=3783677

In the fight against viral infection, host cells can undergo apoptosis prior to viral maturation. This antiviral response curtails the spread of infection to new host cells by preventing the release of viral progeny. A study just published in *PLoS Biology* sheds new light on how one virus, the Epstein–Barr virus (EBV), fights for control of the apoptotic pathways of infected cells, allowing the virus to control the lifespan of the host to complete its replication cycle.

EBV, a tumour-causing herpes virus, targets B cells and establishes a latent infection, a state characterized by the absence of viral replication and the maintenance of the viral genome in the infected cell. During this process, 11 viral genes are expressed that are involved in the establishment of the latent phase of the EBV life cycle. Expression of these genes also contributes directly to B-cell transformation and proliferation, a defining characteristic of EBV infection. As well as the 11 'latency' genes, the virus encodes more than 80 additional genes, including two homologues of cellular *Bcl-2* (*vBcl-2*) which, in other viruses, have been shown to block apoptosis and the subsequent premature death of the host cell. In this study, Markus Altmann and Wolfgang Hammerschmidt investigated the role of these two genes — *BHRF1* and *BALF1* — in the initiation and maintenance of latent EBV infection. The authors constructed mutant virus in which both genes were inactivated. Primary resting B cells infected with the mutant virus did not enter the cell cycle and underwent immediate apoptosis, inhibiting the ability of the virus to establish latent infection. Inactivation of the *vBcl-2* genes also



prevented the virus from transforming B cells. Analysis of *BHRF1* and *BALF1* gene expression by RT-PCR revealed that both genes were maximally expressed in the initials stages of infection but were neither expressed nor required once latent infection had been established. Taken together, these results show that the early and transient expression of the two *vBcl-2* genes prevents the EBV-infected B cells from undergoing apoptosis. By keeping their host cells alive during the early stages of infection, EBV is able to activate and express the other latency genes that allow the virus to persist and begin the process that ultimately leads to cellular transformation and EBV-associated B-cell lymphomas.

The findings presented in this study are the first to demonstrate a direct role for vBcl-2 proteins in latent viral infection. Interesting questions for future investigation include the role of vBcl-2 homologues in other viruses that establish latent infection as part of their life cycle. Future studies can also begin to explore the molecular mechanisms that regulate expression of *BHRF1* and *BALF1*, knowledge that could potentially lead to a new generation of antiviral strategies.

David O'Connell

ORIGINAL RESEARCH PAPER Altmann, M. & Hammerschmidt, W. Epstein–Barr virus provides a new paradigm: a requirement for immediate inhibition of apoptosis. *PLoS Biol.* **3**, e404 (2005)
FURTHER READING Benedict, C.A. *et al.* To kill or be killed: viral evasion of apoptosis. *Nature Immunol.* **3**, 1013–1018 (2002)
WEB SITE
Wolfgang Hammerschmidt's laboratory: http://www3.gsf.de/GENV