IN BRIEF

NUCLEAR TRANSPORT

An essential nuclear envelope integral membrane protein, Brr6p, required for nuclear transport.

de Bruyn Kops, A. & Guthrie, C. *EMBO J.* **20**, 4183–4193 (2001)

Although the role of the nuclear pore complex in nuclear transport is becoming well established, whether the nuclear envelope is involved is unclear. de Bruyn Kops and Guthrie report the first example of an essential yeast gene, *Brr6*, whose product (Brr6) behaves like an integral membrane protein but specifically affects transport of messenger RNA and a protein containing a nuclear export signal. They hypothesize that Brr6 is located adjacent to the nuclear pore and interacts with the pore and transport machinery.

DNA REPAIR

Structure of the Ku heterodimer bound to DNA and its implications for double-strand break repair.

Walker, J. R. *et al. Nature* **412**, 607–614 (2001)

The Ku heterodimer (Ku 70 and Ku 80 subunits) maintains genomic integrity by its ability to bind double-stranded DNA breaks and facilitate their repair. The authors have solved its crystal structure and find the binding site can cradle two full turns of DNA while encircling only the central 3–4 base pairs. Ku makes no contact with the DNA bases but fits sterically to the contours of the major and minor grooves to position the DNA helix in a defined path through the protein ring. These features seem well designed to support broken DNA ends and aid ligation.

SIGNAL TRANSDUCTION

Gibberellins signal nuclear import of PHOR1, a photoperiod-responsive protein with homology to *Drosophila* armadillo.

Amador, V. *et al. Cell* **106**, 343–354 (2001)

The formation of tubers by some species of potato requires short days and decreased signalling by gibberellins (GA). The authors of this paper have now cloned *photoperiod-responsive 1* (*PHOR1*), which is upregulated under short-day conditions. *PHOR1* encodes an armadillo-repeat-containing protein that is rapidly translocated to the nucleus in response to gibberellin application, suggesting that PHOR1 operates in a gibberellin signalling pathway.

CELL ADHESION

Integrin-specific activation of Rac controls progression through the G1 phase of the cell cycle.

Mettouchi, A. *et al. Mol. Cell* **8**, 115–127 (2001)

In the presence of growth factors, endothelial cells undergo cell-cycle arrest when plated on laminin, but proliferate on fibronectin. This new study shows that on fibronectin, mitogens can mediate Rac activation, resulting in cyclin-D1 accumulation and subsequent G1 to S progression. Adhesion to laminin doesn't mediate Rac activation, indicating that Rac might couple signals generated by specific integrins and mitogens to the cell-cycle machinery.

ONCOGENES

The weakest link?

Viruses are cunning — they use altered aspects of transformed cells to facilitate cell infection. This is now backfiring, however, as researchers are exploiting this property to develop anti-cancer therapeutics. To further this research, it is important to know which features of transformed cells aid permissiveness to infection. To this end, Lee and co-workers, in the August issue of *Nature Cell Biology*, showed that an activated Ras pathway (found in many cancer cells) switches off the host-cell anti-viral mechanism, thus increasing infection by herpes simplex virus 1 (HSV-1).

The authors initially compared the level of viral infection in untransformed NIH-3T3 cells with that in cells transformed with oncogenes that activate the Ras pathway — v-*erbB*, *sos* and *ras*. Only transformed cells show significant morphological changes related to infection, such as cell rounding and clumping, and high levels of viral protein synthesis and viral progeny. Interestingly, this was specific to the Ras pathway and was not a general feature of the transformed phenotype, as cells transformed with c-*myc* did not have an increase in viral output. The demonstration that inhibitors of Ras and Mek1/2 — a downstream effector in the Erk pathway — prevented this increase in infection by HSV-1 further proved that an activated Ras pathway is important for infection.

As Ras is a key regulator of several signalling pathways, Ras effector mutants that activate just one pathway — Raf/Erk, phosphatidylinositol 3-kinase and RAL/GDS — were used to see which pathway was involved in permissiveness to infection. The authors showed that activation of the Raf/Erk pathway was the only one that markedly increased susceptibility to HSV-1.

To identify where Ras acts in the infection cycle, the authors used quantitative polymerase chain reaction to investigate which of the genes were transcribed. The early α-gene transcripts were present at equal levels in both *ras*-transformed and untransformed cells, but the later β- and γ-gene transcripts were present at higher levels in the *ras*-transformed cells. As the α-proteins are needed for transcription of the β- and γ-proteins, it is possible that the α-proteins are not translated in the untransformed cells; this was confirmed by western blots.

A well-known anti-viral strategy is phosphorylation of the double-stranded RNA-activated protein kinase (PKR), which leads to inhibition of the translation initiation factor eIF2α, and subsequently translation. *In vitro* kinase assays showed that PKR phosphorylation is more pronounced in untransformed cells as compared with *ras*-transformed cells. The Ras pathway can therefore inactivate the PKR mechanism of the cell to facilitate HSV-1 infection.

HSV-1 mutants, such as G207, are now being tested in clinical trials for anti-cancer activity. R3616, which is similar to G207, is an HSV-1 mutant that is deleted for the viral anti-PKR gene, γ134.5. The R3616 mutant infects *ras*-transformed — but not untransformed — cells, which suggests that the Ras-signalling pathway compensates for the loss of the virus's own anti-PKR mechanism. Confirming the role of PKR in this pathway, mouse embryonic fibroblasts (MEFs) that were deleted for PKR could be infected by the mutant virus whereas parental MEFs remained nonpermissive.

HSV-1, therefore, predominantly uses the host anti-PKR mechanism to infect transformed cells, and its selectiveness for transformed cells makes it a good candidate for an anti-cancer therapeutic. This study not only provides knowledge of the mechanism behind host-cell permissiveness, but also indicates which patients with cancer might benefit from treatment with oncolytic viruses.

Emma Greenwood,
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References and links

ORIGINAL RESEARCH PAPER Farassati, F. *et al.* Oncogenes in Ras signalling pathway dictate host-cell permissiveness to herpes simplex virus 1. *Nature Cell Biol.* **3**, 745–750 (2001)