CELL BIOLOGY

Virus receptors as permeases

Richard G. Vile and Robin A. Weiss

KIM *et al.* and Wang *et al.*, on pages 725 and 729 of this issue[1,2], and B. O'Hara at a recent Cold Spring Harbor Laboratory conference, report that two retroviruses use cell-membrane permease proteins to gain entry to their target cells. These findings are a landmark in mammalian cell physiology, open a new chapter in research into viral receptors and, because the retroviruses concerned cause leukaemia, may yet reveal new mechanisms of viral pathogenesis.

Viruses exploit cellular surface molecules as receptors for binding and entry into host cells. Two approaches have been particularly productive in identifying such receptors — antibodies to cell-surface antigens have been used to block viral attachment or infectivity, and DNA transfer has been used to recover genes which confer infectivity by the virus to otherwise non-permissive cells. Thus CD4 was first identified as the receptor for human immunodeficiency viruses by screening antibodies to leukocyte antigens and, later, when the complementary DNA for CD4 was cloned, by DNA transfer. Likewise, further receptors for mammalian viruses have been identified as cell-surface antigens, for example CR2 for Epstein–Barr virus and ICAM-1 for rhinoviruses. In other cases, DNA transfection has brought to light such previously unrecognized molecules as the receptor for poliovirus and those for two retroviruses, ecotropic murine leukaemia virus (MuLV-E)[3] and gibbon ape leukaemia virus (GALV)[4].

The gene for the receptor for MuLV-E (ecoR) encodes a protein of 622 amino acids with 14 potential membrane-spanning domains[3]. Although the protein is not similar in sequence to other known proteins, the transmembrane topology is reminiscent of that of several other membrane transporter proteins, most notably the permeases for arginine, histidine and choline of yeast. Following up this clue, Cunningham's[1] and Kabat's[2] groups searched for a similar transporter function of ecoR.

Both groups now demonstrate that *Xenopus* oocytes injected with ecoR messenger RNA show increased uptake of the basic amino acids L-lysine, L-ornithine and L-arginine. Only in the presence of extracellular sodium were the injected oocytes capable also of transporting the neutral amino acid homoserine. This sodium-independent transport of cationic amino acids closely resembles the properties of a physiologically well-characterized amino-acid transport pathway of mammalian cells, known as y^+ (refs 5 and 6). From the functional data, the largely ubiquitous tissue co-expression of y^+ and ecoR, and the structural similarity to yeast amino-acid transporters, it seems certain that ecoR and y^+ are one and the same, making this the first mammalian amino-acid transporter to be cloned and the first instance of a virus subverting a transmembrane channel protein as a receptor.

Not only will this revelation open up the field of mammalian amino-acid transport physiology, but also, as Wang and colleagues suggest, it may lead to the definition of inherited genetic diseases caused by abnormal cellular transport of amino acids (just as the defect in cystic fibrosis is caused by mutations to a putative chloride transporter). Cell physiologists may also be able to benefit from the work already performed on the pathways of viral entry following binding — the methods by which virus–receptor complexes are recruited into coated pits (receptor-mediated endocytosis) or fuse to the cell membrane after binding should help in unravelling the normal processes involved in turnover of these transporter proteins at the cell surface[7,8].

Last year, a cDNA that confers susceptibility to infection by GALV was cloned, the predicted protein sequence being 679 amino acids in length, containing membrane-spanning domains and having no detectable sequence similarity to other known proteins[4]. Now, O'Hara and colleagues (Lederle laboratories,

Snap, crackle and pop

Gordon Tribble

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

LAVA from the slopes of Kilauea volcano on Hawaii island can flow as far as the sea. Gordon Tribble of the US Geological Survey and colleagues went scuba diving in 1989 to find out its fate. At the time, lava had been flowing continuously from the eastern flanks of the volcano for two years. It reached the coastal edge 12 kilometres away through shallow tubes encased within the older, cooled lava, making hot fire spouts that drained straight into the sea. The divers' efforts were rewarded by the observation of a new type of lava flow, streams about a metre wide that advanced at a speed up to 3 metres a second down the steep submarine slopes. Although they could not trace the lava so far, the researchers suggest the streams could plunge to depths of 100 metres or more. At times, Tribble's description of the dives (*Geology* **19**, 633–636; 1991) reads like a boys-own adventure. One colleague was buried up to his knees as rocks and debris slumped down the steep submarine slope. "Frequent loud popping sounds were superimposed on a constant background noise of sizzling and cracking" Tribble records. "Resonant booms and concussions punctuated the activity." Much of this noise Tribble associates with the occurrence of fissures in the cool crust overlaying the streams, like that shown here, in which water became heated. The gas bubbles that emerged from the lava (some looking like 30-centimetre smoke rings) contained not only steam, but also hydrogen and oxygen from thermally dissociated water, which could spontaneously combust. □