## Xenotransplanters Turn Xenovirologists

SIGHTINGS

Donor organs for transplantation are scarce, and this shortage has stimulated academic and commercial interest in techniques that employ animals as potential organ sources. One approach rapidly gaining ground is the use of pig organs for human transplantation. Though promising, pig xenotransplantation has a serious problem: hyperacute rejection (HAR) caused by preexisting human antibodies.

Pigs produce a specific sugar (α-gal) on the surface of their cells that is not found in human cells (or any other Old World primates). Consequently, all humans have existing antibodies that will target any α-gal–coated cells for destruction. Methods to either remove the HAR antibodies or decrease the expression of α-gal in the donor organ have reduced the severity of rejection and thus make xenografting a real possibility. Recent findings, however, show that there is a catch. Patience *et al.* (*1*) have discovered that pigs harbor endogenous retroviruses (PERV) that are capable of infecting human cells in vitro.

The normal germ line DNA of many vertebrates contains endogenous retroviruses (ERV) that act as molecular parasites, propagating via germline transmission and, if functional, through a productive infection as well. Some ERV can cause diseases such as leukemia, while others appear innocuous. Cross-species transmission of ERV from some animals such as cats (RD114) and baboons (BaEv) to humans has been shown to occur in the lab (*2*).

Given these data, it is a disturbing possibility that pig retroviruses might infect human cells following xenotransplantation. Patience *et al.* studied this by first confirming the existence of pig retroviruses in two commonly used pig cell lines, PK-15 and MPK. Electron microscopy showed the characteristic morphology of C-type retroviruses. Using supernatants from PK-15 and MPK cell cultures to infect human cell lines in vitro, they showed that PK-15 (but not MPK) -derived virus could infect the human kidney cell line 293. By cocultivating PK-15 with human cells, they then could infect a broader range of human hosts that included lines from lung (MRC-5), muscle (RD), and lymphoid (Raji, SupT1, and Molt4) origin. The message seems to be that productive pig-to-human viral infections can occur in the laboratory and that cell-cell contact increases their likelihood. Whether they occur in vivo is largely unknown.

The study went on to use degenerate PCR oligo primers directed at the conserved region of known retroviral proteases and reverse transcriptases to actually clone the PERV from both PK-15 and MPK cell lines. Both PERVs turn out to have more than 95% sequence similarity to each other and a strong identity to the gibbon ape leukemia virus (GALV). By blotting the cloned viral genomes to Southerns of normal pig tissue (from heart, kidney, and spleen), the investigators showed conclusively that the PERVs are indeed endogenous. The data were far from subtle: More than 50 complete or partial copies of PERV were shown to exist per swine genome.

Taken together, these results point out the surprises and challenges of working with an experimental system as complex as a whole animal. Just when promising strategies were developed to circumvent the rejection of xenografts, the specter of producing novel viral infections in the recipient has arrived. One solution could be to breed pig stocks that lack any known endogenous viruses. This will not be trivial given the abundance of integrants in the genome. Even more alarming is the possibility that unidentified pig DNA or RNA viruses exist in a human transmissible form. The question of whether endogenous viruses can escape the radar screen of present day detection techniques remains an open one.

### References


1. C. Patience *et al.*, *Nature Med.* **3**, 282 (1997).
2. R. E. Beneviste *et al.*, *Nature* **248**, 17 (1974); R. M. McAllister *et al.*, *Nature New Biol.* **235**, 3 (1972); J. M. Coffin, in *RNA Tumor Viruses*, R. A. Weiss, H. E. Varmus, N. M. Teich, J. M. Coffin (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1985).



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