Virology

A new package for an old oncogene

from William D. Hardy Jr

PET cats develop retrovirus-induced lymphoid malignancies more frequently than any other mammal. The aetiological agent of feline lymphoid tumours is the feline leukaemia virus (FeLV), a highly contagious chronic leukaemia virus that induces both FeLV-positive and FeLV-negative lymphosarcomas. Like other chronic leukaemia viruses, and in contrast to acute leukaemia viruses, FeLV does not possess a transforming gene (oncogene) and induces leukaemia only after a long period of latency. But among the chronic leukaemia viruses of mammals, FeLV has a unique propensity to recombine with a variety of cellular sequences, thereby being converted into a variety of acute transforming feline sarcoma viruses distinguished by the oncogene they carry. Now, on pages 814, 853 and 856 of this issue of *Nature*, three independent groups report finding defective FeLV proviruses containing the *myc* oncogene in the DNA of 8 of 58 pet cats with naturally occurring FeLV-positive thymic lymphosarcomas and provide some evidence to suggest that a *myc*-containing leukaemia virus may be transmitted contagiously between cats[1-3]. If so, it would provide the first example of a naturally occurring oncogene-carrying leukaemia virus of mammals.

All acute transforming sarcoma and leukaemia viruses have been identified and isolated by virtue of their ability to transform fibroblasts and/or haematopoietic cells in culture[4]. Since FeLV derived from feline lymphosarcomas does not transform cells *in vitro*, the three groups used *myc* probes and Southern blot analysis to study the cat c-*myc* locus in lymphosarcoma DNA[1-3]. In order to show that the novel *myc* sequences found were encapsidated in functional viruses the Neil[1] and Mullins[2] groups inoculated feline embryo cells either with supernatant from cultured thymic lymphosarcoma cells or with blood plasma from cats with thymic lymphosarcomas. After inoculation the DNA of the embryo cells was extracted and digested with the restriction enzyme *Kpn*I. Since *myc* fragments of proviral origin can be distinguished from those of the cellular *myc* gene, it was possible to prove that the embryo-cell DNA contained *myc* sequences that were derived from viruses in the supernatants or plasma even though the cells showed no evidence of morphological transformation. This finding raises the possibility that *myc*-containing FeLVs may be transmitted contagiously among pet cats rather than generated *de novo* in each case.

It should be noted that the occurrence of *myc*-containing FeLVs varied markedly between the three studies. Neil's group found evidence of c-*myc* alteration in four of nine naturally occurring FeLV-positive lymphosarcomas, in one of seven FeLV-negative lymphosarcomas, in two of three T-cell lymphosarcoma cell culture lines and in two of four experimentally induced thymic lymphosarcomas[1] whereas the Levy and Mullins groups, combined, found *myc*-containing proviruses in only three of sixty-one naturally occurring lymphosarcomas[2,3]. These variations may represent the different extent of contagious spread of such viruses in Scotland[1] and the United States[2,3], or the selection of certain tumour types (thymic lymphosarcomas) by the Scottish group and not by the others.

Most naturally occurring leukaemias of animals are caused by contagiously transmitted chronic leukaemia viruses. Although the chronic leukaemia virus, avian leukaemia virus, induces bursal lymphomas in chickens via integration close to, and activation of, c-*myc*[5] (which, in some way, leads to activation of a second oncogene, *B-lym*[6]), there is so far no evidence of oncogene activation by a chronic leukaemia virus in any naturally occurring mammalian leukaemia. In one mammal, the mouse, however, there is suggestive evidence of a related process in the form of *env* gene recombinant chronic leukaemia viruses. Three classes of murine leukaemia viruses (MuLV) can be distinguished on the basis of their host range in tissue culture which is determined by the viral *env* gene[7]. These are: ecotropic, which replicate only in murine cells; xenotropic, which replicate primarily in heterologous cells; and mink cytopathic focus-forming (MCF) viruses, which replicate in both murine and heterologous cells. MCF viruses are recombinants between ecotropic MuLV and endogenous *env* sequences related to xenotropic viruses[8,9]. DNA of embryo AKR mice (high leukaemia strain) contains about 10 non-tandem copies of intact MCF-like *env* gene sequences with a proviral structure[10]. In spontaneous AKR thymic lymphosarcomas, these MCF-like *env* sequences are regularly found to have recombined with a specific region of the 3′ end of the ecotropic *env* gene. This specific recombination appears to be the proximal event in the induction of AKR lymphomas and chronic viraemia is probably needed to generate the leukaemogenic MCF recombinant virus.

There is recent intriguing evidence for the existence of MCF-like *env* gene recombinant FeLVs. Elder and Mullins have shown a striking resemblance between the nucleotide sequences of the envelope genes of subgroup FeLV-B and a Moloney virus-derived MuLV MCF virus[11]. Both FeLV-B and MCF-MuLV can infect cells of various species, whereas FeLV-A and ecotropic MuLV usually only infect cat and mouse cells respectively. Cellular DNA of normal uninfected cats contains multiple copies of sequences that are related to the genome of contagious exogenous FeLV[12-14], although these exogenous sequences cannot be induced to become infectious viral particles[12]. Recently, the endogenous sequences have been shown to be significantly shorter than the exogenous infectious FeLV genome[15] but with only a small deletion in the *env* region. It is possible that these endogenous *env* sequences may recombine with exogenous FeLV and form recombinant FeLV–*env* gene products. Recent data[16] from this institute suggest recombination of that type as the best explanation for the presence of the FeLV-induced tumour-specific antigens on the cell surface of all feline lymphosarcomas[17].

It is tempting to speculate that there may be a relationship between the generation of *env* gene recombinant FeLVs and oncogene activation. In this regard, Cloyd has found that lymphomagenic MCF viruses of thymic origin, AKR-247 and C58L1, replicate selectively in immature lymphocytes present only in the thymic cortex of mice[18]. One might postulate that similar *env* gene recombinant FeLVs infect only a subset of lymphocytes, those with specific receptors for the protein products of the recombinant genes, and that integration of the FeLV provirus in members of this subset might lead to leukaemogenesis by activation or alteration of c-*myc* or some other cellular oncogene. Further studies of FeLV-induced lymphoid tumours of pet cats may give us a clearer picture of the importance of oncogene-containing acute leukaemia viruses and *env* gene recombinant chronic leukaemia viruses in leukaemogenesis. □

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William D. Hardy Jr is an Associate Member in the Memorial Sloan Kettering Cancer Center, Cornell University, New York, NY 10021.