

Tumor-Prone Mice—and *myc*

Mice that have been genetically altered by addition of a modified myc oncogene have a strong tendency to develop cancers

A modified version of the *myc* oncogene has been introduced into the germ lines of mice, which subsequently displayed an inheritable tendency to develop cancers. Speaking at the Seventh Annual Bristol-Myers Symposium on Cancer Research,* Philip Leder of Harvard Medical School said that the genetically altered mouse strains thus produced provide a way of studying in living animals the effects of a gene that has been linked to the development of human and murine cancers, especially lymphomas.

The gene used in the experiments,† which Leder and Timothy Stewart of Harvard performed in collaboration with Paul Pattengale of the University of Southern California, was a hybrid constructed by replacing the control regions of the normal mouse *myc* gene with a control sequence from the mouse mammary tumor virus (MMTV). "The gene from a normal mouse should code for a normal protein product," Leder notes.

Stewart injected the hybrid gene into fertilized mouse eggs, which were then implanted in foster mothers to develop. Ten of the animals that were eventually born carried the transferred gene sequences. In some of these "transgenic" mice (so-called because they carry a transferred gene) the gene is expressed in only one or a few tissues, but in others it is more widely active. One animal showed evidence of the gene activity in all the tissues examined.

When the transgenic mice were bred, the females showed a strong tendency to develop malignant breast tumors during their second or third pregnancies. This is true both for the original founder animals, two of which have now developed the tumors, and for their progeny. "Four of the five female progeny of one founder animal inherited the gene and three of these developed adenocarcinoma of the breast," Leder says. The fourth daughter with the inherited gene was not bred.

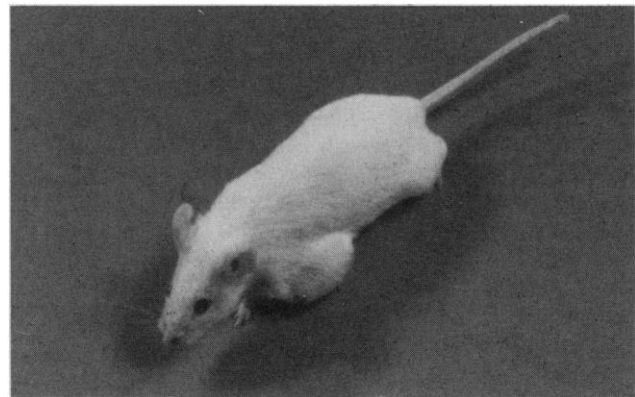
The founder animal of a third line of transgenic mice has not yet developed cancer, but one of its female progeny has both the breast cancer and a lymphoma and two other progeny have tumors that are probably lymphomas.

"It seems that these animals are tumor-prone. They inherit the propensity to develop these malignancies from their parents," Leder concludes. Animals that received a copy of the mouse *myc* gene with its own control sequences have not yet shown any signs of developing cancers.

It is perhaps not surprising that the females develop the breast cancer during pregnancy. The MMTV control sequence used, which was supplied to the Leder group by Gordon Hager of the National Cancer Institute, responds to lactation hormones by stimulating expression of the gene to which it is connected. Both the tumors and the normal lactating breast tissue showed high expression of the hybrid gene. This suggests that high production of the

normal *myc* product contributes to the development of the cancer but is not sufficient by itself. "The entire breast is not transformed even though the entire breast is expressing the gene," Leder told the symposium participants. "We expect that some other event is also necessary." The findings are consistent with the current view that aberrant *myc* expression contributes to carcinogenesis by helping to keep cells in a persistently dividing state but that additional activated oncogenes are needed for full transformation to malignancy.

There is a caveat about attributing the breast and other tumors to expression of the transferred *myc* sequences. The investigators have not yet tried injecting fertilized mouse eggs with just the MMTV promoter. There is a chance that this sequence, which can increase gene expression, could transform cells on its own, without the transferred *myc* sequences, by integrating near one the cellular oncogene counterparts and activating it.



Tumor-prone mouse

A mouse that has inherited a transferred myc oncogene with an MMTV promoter has developed a large breast cancer.

Leder thinks this to be highly unlikely, however. The transferred MMTV promoter did not appear to be increasing the expression of any cellular genes. The investigators detected RNA transcripts containing transferred MMTV promoter sequences only in conjunction with *myc* RNA. Moreover, three of the mouse lines that have been produced by animals carrying the hybrid gene have already shown the strong tendency to develop cancers. In view of the fact that the transferred sequences can integrate anywhere in the genome, it is not very probable that the MMTV promoter would land near an endogenous oncogene so frequently. "It would be like hitting the New York State lottery several times in a row," Leder notes.

In addition to studying *myc* gene activity directly in the transgenic animals, their tissues may also be used for producing lines of cultured cells from a variety of tissues in which the *myc* gene is already activated. Such cells would be useful, among other things, for studying the interaction of *myc* with other oncogenes.—JEAN L. MARX

*Organized under the aegis of Memorial Sloan-Kettering Cancer Center and held at Rockefeller University on 8 and 9 October.

†T. A. Stewart, P. K. Pattengale, P. Leder, *Cell* 38, 627 (1984).