INTERNATIONAL ASSOCIATION FOR BREAST CANCER RESEARCH

Breast Cancer Research Conference

Abstract

Denver, Colorado

March 20 - 24, 1983

ONCOGENESIS WITHOUT VIRAL ONCOGENES BY AVIAN LEUKOSIS AND MOUSE MAMMARY TUMOR VIRUSES

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We have been exploring the behavior of certain oncogenic retroviruses that lack their own oncogenes but can activate cellular genes by insertional mutation. In B cell lymphomas induced in chickens by avian leukosis virus (ALV), an elevated level of expression of a cellular oncogene (c-myc), is observed with three different arrangements of integrated ALV DNA within the c-myc locus (1). The results imply that proviral DNA can activate expression of host genes either directly, by providing a viral promoter, or indirectly, by affecting the efficiency of a host promoter. Analysis of DNA cloned from interrupted c-myc loci in B cell lymphomas and studies of the expression of the herpes simplex virus thymidine kinase gene joined in vitro to retroviral DNA (2) indicate that retroviral sequences sufficient for both the direct and indirect mechanisms lie within or immediately adjacent to an LTR. Related mechanisms appear to operate during oncogenesis by the mouse mammary tumor virus (MMTV). Most of the MMTV-induced mammary tumors in C3H mice harbor proviral DNA within a 20 kb domain of the mouse genome that we have called int-1 (3). The insertions occur in several clusters throughout this region, on both sides of a transcriptional unit that is silent in normal mammary glands but expressed at a low level in tumors with an interrupted int-1 locus. We interpret these findings to mean that rare insertions of MMTV DNA into int-1 can initiate tumorigenesis by activating a heretofore unrecognized cellular oncogene.

1. G.S. Payne, J.M. Bishop and H.E. Varmus. Nature 295:209-217, 1982.
2. P. Luciw, J.M. Bishop, H.E. Varmus and M. Capecchi. Cell, in press.
3. R. Nusse and H.E. Varmus. Cell 31:99-109, 1982.