Cancer Cell Genes Linked to Viral *onc* Genes

Some of the transforming genes found in human cancer cells may be identical to the well-studied oncogenes of animal cancer viruses

Developments of the past few months reveal that cancers of viral and nonviral origin could have more in common than was once thought. Both may be caused by the inappropriate activation of similar—perhaps identical—cellular genes.

Using gene transfer methods, investigators recently detected genes that induce the cancerous transformation of cultured mouse cells in DNA from human and other animal cancers, which either arose spontaneously or were chemically induced (*Science*, 19 February, p. 955). The properties of these transforming genes parallel those of the *onc* (for oncogenic) genes of the RNA-containing tumor viruses of animals.

Both types of genes are potently oncogenic and both appear to have their origins in cellular gene sequences. The viral *onc* genes are derived from normal cellular genes, sometimes called proto-oncogenes, which acquired the ability to transform when they were picked up by the viruses. The transforming genes of the cancer cells also have normal counterparts and are thought to have arisen as the result of some as yet unidentified alteration of the normal genes.

These findings raised an obvious question: Are any of the transforming genes found in the cancer cells related to any of the viral *onc* genes? The answer is turning out to be yes, according to results presented at two meetings* by four different groups of investigators.

There are about 15 viral *onc* genes, of which two related sarcoma genes have been found to resemble oncogenes from human cancer cells. These resemblances have been detected by using probes, DNA copies of the RNA *onc* genes, to look for corresponding DNA segments in mouse cells transformed with cancer cell DNA. Luis Parada and Robert Weinberg of the Massachusetts Institute of Technology found that cells transformed by DNA from the EJ line of human bladder carcinoma cells contained a novel DNA fragment that reacted with a probe for the *ras* oncogene of the Harvey strain of murine sarcoma virus. "This leads to the conclusion," Weinberg told the Gatlinburg symposium, "that the oncogene acquired by Harvey sarcoma virus is related to the oncogene of the bladder carcinoma. The implications are exciting. The same proto-oncogene can be activated by two methods—by acquisition by a tumor virus or by some kind of somatic mutation."

The *bas* gene, which is present in a sarcoma virus that causes cancers in BALB/c mice, is nearly identical to the *ras* gene. It is not surprising, then, that Mariano Barbacid and Eugene Santos of the National Cancer Institute found the transforming gene of the T24 line of human bladder carcinoma cells to be closely related to the *bas* gene. Work by Weinberg's group and that of Michael Wigler at Cold Spring Harbor Laboratory had already suggested that the EJ and T24 transforming genes might be identical.

The earlier assumption, that the same transforming gene was activated in two independently derived cell lines, now appears to be in doubt, however, as work by Wigler's group suggests that the EJ and T24 lines may not be different after all. This could mean that the transforming gene is peculiar to just one type of cultured bladder carcinoma cell, although recent work by Barbacid and his colleagues indicates otherwise. They have evidence for the presence of the same transforming gene in a primary human bladder carcinoma.

The relation between the bladder-transforming gene and the Harvey *ras* gene was also observed by Wigler and by Geoffrey Cooper and his colleagues at Harvard Medical School and the Sidney Farber Cancer Institute. In addition, Cooper with Channing Der and Theodore Krontiris, also of Sidney Farber, found that the transforming gene from a line of human lung carcinoma cells is structurally similar to the *ras* gene of the Kirsten strain of murine sarcoma virus. The Harvey and Kirsten *ras* genes diverged more than 600 million years ago and their structures are dissimilar, although their protein products resemble one another. Previous analyses had shown the lung gene to be different from that of the bladder but the same as the transforming gene detected in colon carcinoma cells.

Cooper points out, "Three of four human carcinomas have oncogenes corresponding to a *ras* gene—the bladder oncogene to Harvey *ras* and the lung-colon gene to Kirsten *ras*." Moreover, according to results presented at the Frederick workshop by Mitchell Goldfarb of Wigler's laboratory, the transforming gene of a neuroblastoma cell line has resemblances to both the Kirsten and Harvey *ras* genes. The oncogene found in the fourth type of human carcinoma cells, a line derived from a mammary cancer, does not appear so far to correspond to any of the known viral *onc* genes.

Other, still undetected, oncogenes may exist, however. Weinberg, for one, speculates that the *ras* family may have more members. He suggests that "all the oncogenes may have descended from two or three ancestral genes that diverged during evolution."

The nature of the changes that convert the proto-oncogenes of normal cells to the activated oncogenes of cancer cells or viruses remains a puzzle. Gene rearrangements, possibly resulting in aberrant control of gene expression, have been prominently mentioned as a possible cause. So far, none of the investigators mentioned here have found any indication of major rearrangements when they compared restriction maps of the transforming genes with those of their normal cellular counterparts. Barbacid, for example, cloned the normal analog of the T24 gene and compared it with the transforming gene. He did not observe any differences between them. Nevertheless, both the T24 and *bas* oncogenes transform cells, whereas the normal gene does not. Barbacid says, "The cautious conclusion is that whatever rearrangement or substitution has occurred is very minor. The only way to find out the difference is by sequencing the genes."

Sequencing is high on everyone's agenda of what to do next. So is identification of the gene products and determination of how they work. Researchers would also like to reconcile the vast body of evidence that human cancers develop naturally in several steps, which often take years, with the observation that the transforming genes, viral and otherwise, seem to work in one step.

—JEAN L. MARX

*The Symposium on Genetic Mechanisms of Carcinogenesis was organized under the auspices of Oak Ridge National Laboratory and held on 11 to 15 April in Gatlinburg, Tennessee and the Workshop on Gene Transfer and Cancer was held on 16 to 18 April at the Frederick (Maryland) Cancer Research Facility of the National Cancer Institute.

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