The N-*myc* Oncogene in Neural Tumors

Two human neural tumors show increased numbers or expression of the N-myc gene. Does activation of the gene contribute to the cancers' development?

Although a great deal of research has shown that the two dozen or so oncogenes can cause cancers in animals and produce the malignant transformation of cultured cells, there is little direct evidence implicating the genes in the development of human cancers. Two reports, one in this issue of *Science* and another in the 31 May issue of *Nature*, add to that small, but growing, body of evidence. Both suggest a possible participation of a member of the *myc* gene family in the development of neuroblastomas and retinoblastomas, tumors of neural tissue that usually occur in infants or young children. The gene may act differently in the two tumors, however .

Garrett M. Brodeur of Washington University School of Medicine and his colleagues* have found that nearly 40 percent of 63 neuroblastoma tumors contain many extra copies of the N-*myc* gene. Within the past year, such amplification of N-*myc* and other oncogenes has been detected in tumor cells of a variety of different types, including neuroblastomas (*Science*, 6 January, p. 40). Many of the cells used for the original experiments had been maintained in culture, and the amplification might have occurred after removal from the patients. But the 63 neuroblastomas examined by Brodeur, Robert Seeger of the University of California School of Medicine in Los Angeles, and their collaborators in the Children's Cancer Study Group (CCSG) were primary tumors that had been surgically removed from patients who had not previously undergone chemotherapy or other treatments.

Moreover, the presence of the amplification correlates with the stage of the tumors, which is one of the best indicators of the patient's prognosis. About 75 to 90 percent of patients with stage 1 or 2 neuroblastomas, which have not yet spread to distant tissues, survive for 2 years without recurrence of the disease. The comparable figures for children with cancers that have spread range from 30 percent for those with stage 3 tumors to only 15 percent for those with stage 4 tumors. "It was clear that low-stage patients with good prognoses did not have the amplification," Brodeur says. "But about half of the higher stage patients with poor prognoses did have it."

Brodeur and Seeger now plan a progressive study to determine whether the presence of the N-*myc* gene amplification means that the patients have an even worse prognosis than others of the same advanced stage. Preliminary analysis by the CCSG of survival data for patients with advanced disease suggests that this is the case. If these studies are confirmed, then it is likely that in the future the presence or absence of N-*myc* amplification would influence the therapies given the patients.

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In a related development, William F. Benedict, Wen-Hwa Lee, and A. Linn Murphree of the Children's Hospital of Los Angeles and the University of Southern California School of Medicine† have found that two of ten retinoblastoma tumors, all of which were small primary tumors, and also a line of cultured retinoblastoma cells, show amplification of the N-*myc* gene. In addition, all of the cells had increased expression of the gene, as determined by measuring the messenger RNA transcripts of N-*myc*. "Even though you don't have the gene amplified you do see increased expression," Benedict notes.

This result is somewhat surprising. Previous work had demonstrated that gene amplification and increased expression generally go hand in hand, but Benedict did not expect to find N-*myc* expression increased in all the tumors. Brodeur and his colleagues are now determining whether expression of the gene is increased in neuroblastoma tumors that do not have amplification.

If these tumors do not have increased expression, then the results of the two groups imply that N-*myc* may work differently in retinoblastomas than in neuroblastomas. "Because you see increased expression in the small, primary tumors, it is possible that it may be involved in the etiology of the disease," Benedict comments. There is an important caveat, however. N-*myc* was originally identified in cells because of its resemblance to another member of the family, the viral *myc* gene, which was itself identified as the oncogene of the animal cancer virus MC29. But the oncogenicity of N-*myc* has not been directly demonstrated. It is assumed on the basis of its resemblance to the viral *myc*, although finding evidence of N-*myc* activation in the two types of tumor lends additional support to the idea.

In contrast, amplification of the gene in neuroblastomas appears to have more to do with progression of the tumor to a more malignant state than with transformation itself. As Brodeur points out "The fact that over half the tumors do not have genomic amplification suggests that it is not a primary event. It may be a secondary event associated with rapidly progressive disease."

This finding resembles one already reported for small cell carcinoma of the lung (SSLC) by John Minna and his colleagues at the Naval Medical Center in Bethesda, Maryland, and the National Cancer Institute. They found that amplification of another *myc* family member, this one the cellular gene from which viral *myc* is probably derived, correlated with an extremely malignant variant type of SCLC cell. More recently they have also detected amplification of N-*myc* in SCLC cells, which, their name notwithstanding, have some of the biochemical characteristics of nerve cells.

Both neuroblastomas and retinoblastomas are associated with deletions of specific chromosomal regions. In the neuroblastomas, the deletion removes part of chromosome 1. The connection between this abnormality and N-*myc* amplification, if any, is unclear. According to Benedict and Murphree, the loss or inactivation of a gene on chromosome 13 contributes to the development of retinoblastoma. They have postulated that the normal function of this gene is the suppression of some other gene, which may have a normal function in embryonic development, but which might have an oncogenic potential if expressed in more mature cells. Although there is currently no evidence that the gene on chromosome 13 acts to keep N-*myc* in check, that is a logical hypothesis to test.

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*G. M. Brodeur, R. C. Seeger, M. Schwab, H. E. Varmus, J. M. Bishop, *Science*, this issue, p. 1121.

†W.-H. Lee, A. L. Murphree, W. F. Benedict, *Nature (London)* **309**, 458 (1984).