Oncogene Linked to Growth Factor Receptor

The viral oncogene, erbB, may be derived from the cellular gene for epidermal growth factor, or at least from a very similar cellular gene

The theory that oncogenes—genes that cause the cancerous transformation of cells—are derived from normal cellular genes that regulate cell division and differentiation has received another boost. Investigators have now found that one of the hitherto lesser known viral oncogenes, namely *erb*B, may be derived from the gene coding for the receptor for epidermal growth factor (EGF).* At very least it is derived from a gene closely related to that for the receptor.

*Erb*B is the second viral oncogene to be linked to the function of a growth factor. Last summer, two groups found that the product of the *sis* gene, the transforming gene of simian sarcoma virus, closely resembles one of the two protein chains composing platelet-derived growth factor (PDGF) (*Science*, 15 July 1983, p. 248). The two sets of results lend credence to the hypothesis that oncogenes may contribute to the development of cancers by subverting the normal growth control mechanisms.

In the current work, investigators from the laboratories of Michael Waterfield of the Imperial Cancer Research Fund in London, Joseph Schlessinger of the Weizmann Institute of Science in Rehovot, Israel, and Axel Ullrich of Genetech, Incorporated, in San Francisco, determined the partial amino acid sequence of the human EGF receptor. To do this, they cleaved the purified receptor molecule, which is a glycoprotein with a molecular weight of 175,000, into smaller peptides and then determined the amino acid sequences of 14 of the peptides.

The nucleotide sequences of many of the 20 or so known viral oncogenes have been determined and can be used to predict the amino acid sequences of their protein products. Waterfield and his colleagues compared these sequences with those of the EGF receptor peptides. Six of the peptides proved to be almost identical to segments of the *erb*B product. "[in the six peptides] 74 of the 83 amino acids are shared with the *erb*B sequences," Waterfield says. "And another four of the amino acids have undergone only conservative changes."

The viral oncogenes are all derived from cellular genes that were picked up by the viruses during the course of infection. The great similarity is especially remarkable in view of the fact that the *erb*B oncogene, which was identified in avian erythroblastosis virus, presumably originated in the chicken, and the EGF receptor was of human origin. "That says that it is a very conserved sequence," Waterfield notes.

The new results strongly suggest that it is the EGF receptor gene that gave rise to *erb*B. In fact, other investigators have mapped both the cellular counterpart of *erb*B and the receptor gene to similar positions on the long arm of human chromosome 7, a finding which supports that idea. However, the possibility remains that chromosome 7 contains a family of genes with similar structures and more work is needed to determine whether the receptor gene itself gave rise to the oncogene or whether it was another cellular gene with a very similar structure.

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There was no resemblance between the amino acid sequences of eight of the EGF receptor peptides and that of the *erb*B protein. This is not surprising because the receptor protein is much bigger than the oncogene product. The *erb*B sequence, which was determined by Tadashi Yamamoto of the University of Tokyo and his colleagues,† codes for a product containing 604 amino acids, roughly half of the approximately 1250 forming the protein backbone of the EGF receptor. (Carbohydrate accounts for about 37,000 and protein for about 138,000 of the total molecular weight of the receptor molecule.)

The EGF receptor consists of three regions. One of these projects outside the cell and contains the site for binding EGF. The second is embedded in the membrane. And the third region projects into the cytoplasm of the cell interior. According to Waterfield and his colleagues, the sequence encoded by *erb*B corresponds to the transmembrane and cytoplasmic portions of the EGF receptor. The gene segment coding for the growth factor binding region was apparently not acquired by the virus.

A few years ago, Stanley Cohen of Vanderbilt University found that the EGF receptor is a kinase enzyme that can attach phosphate groups to tyrosine residues in proteins, an unusual property shared by some half-dozen viral oncogene products. It is apparently the cytoplasmic region that contains the kinase activity of the receptor.

So far no kinase activity has been demonstrated for the product of the *erb*B gene. But the oncogenes that code for known kinase products have certain structural features in common. As it happens, *erb*B has these characteristic features. "It has the whole kinase domain," says J. Michael Bishop of the University of California School of Medicine in San Francisco.

The receptor signals the cell to divide when EGF binds. How it does this is still a mystery. However, Waterfield and his colleagues suggest that *erb*B transforms cells because "the product is a truncated EGF receptor that has lost its binding domain. It might be involved in signal transfer but couldn't be turned off if it lacked the binding domain." As a result, the cells would be continually stimulated to divide. Although avian erythroblastosis virus contains another oncogene, *erb*A, work with mutant virus strains indicates that *erb*B alone is capable of transforming appropriate target cells.

The discovery of the link between the EGF receptor gene and *erb*B is sure to stimulate a great deal of research. As many as half of the known viral oncogenes have either tyrosine kinase activity or the structural features of a kinase. Moreover, the receptors for additional growth-stimulating agents, including the hormone insulin and PDGF, are kinases. *Erb*B may not be the only oncogene to be derived from a growth factor receptor.

The research also shows that there are at least two ways in which an oncogene may act to stimulate cell division. It may code either for a growth factor component, as the *sis* gene does, or it may code for an aberrant growth factor receptor that has lost its normal control sequences, as *erb*B apparently does.

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†T. Yamamoto, T. Nishida, N. Miyajima, S. Kawai, T. Ooi, K. Toyoshima, *Cell* **35**, 71 (1983).