onc Gene Related to Growth Factor Gene

The finding supports the view that an onc *gene may make cells cancerous by inappropriately producing a substance that regulates normal growth*

For the first time, one of the *onc* (for oncogenic) genes carried by the animal cancer viruses has been shown to correspond to a cellular gene of known function. According to a report in this issue of *Science* (p. 275) and another to be published in *Nature*, the *onc* gene of simian sarcoma virus is very closely related to a gene coding for platelet-derived growth factor (PDGF). The finding provides direct evidence that an *onc* gene may contribute to the malignant transformation of cells by inappropriately producing a product that normally stimulates cell growth. "This could be a powerful step to a better understanding of both the normal and abnormal functioning of these genes," says Stuart Aaronson of the National Cancer Institute.

The current development represents an unusual intersection between three previously unrelated lines of research. Harry Antoniades of the Harvard School of Public Health has been studying PDGF for more than 10 years. About 3 years ago, he and his colleagues purified enough of the protein to begin determining its amino acid sequence. This material was given for analysis to Michael Hunkapiller, who works in Leroy Hood's laboratory at the California Institute of Technology.

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The sequence determination performed by Hunkapiller suggested that the PDGF molecule consists of two polypeptide chains that may be homologous in structure. Antoniades and Hunkapiller published partial amino acid sequences of the two chains, now called PDGF-1 and PDGF-2, in the 27 May issue of *Science* (p. 963).

Over the past 5 years Russell Doolittle of the University of California at San Diego has been accumulating a computer bank of protein sequences for his studies of protein evolution. On the Saturday morning after receiving the 27 May *Science*, he typed the PDGF sequences into the home terminal of his computer.

After comparing the new partial sequences with those already stored in its memory, the computer revealed that they closely resemble segments of the protein product of the *onc* gene of simian sarcoma virus (*sis* gene), the sequence of which had previously been determined by the Aaronson group. The resemblance was particularly close for PDGF-2. Eighty-seven percent of the 70 amino acids in the known segments of this polypeptide matched those in the *onc* gene product sequences. "It was not quite a perfect match," Doolittle says, "but very, very close to being an identity. The percent difference was just about what you would expect on the basis of the species difference." The PDGF was isolated from outdated preparations of human platelets whereas the *sis* gene is thought to have originated in the genome of the woolly monkey.

Meanwhile, Michael Waterfield of the Imperial Cancer Research Fund Laboratories, Lincoln's Inn Fields, London, was also working on the structure of PDGF in collaboration with Thomas Deuel of Washington University School of Medicine and Åke Wasteson of the University of Uppsala, Sweden. At present, these investigators conclude, the data are not adequate to determine whether the PDGF molecule consists of two different, but homologous, polypeptide chains or of one chain that has been extensively broken down by proteolytic enzymes. PDGF has been difficult to study, partly because the outdated platelet preparations from which it is purified carry many such enzymes.

In any event, Waterfield and his colleagues have determined the amino acid sequence of a PDGF fragment containing 104 amino acids. They, too, compared it with the Doolittle data base, which he supplies free of charge to nonprofit organizations. Again, the computer showed a close relationship to the *sis* gene product, although the match was not exact. About five of the amino acids from the PDGF sequence were not found in the viral product. The interpretation of this variation depends on the structure of the PDGF molecule. If there is one chain, Waterfield notes, "it is compatible with the possibility that the virus has rearranged some of the sequence. Alternatively, the virus may have acquired the gene for one chain of a two-chain molecule."

The 20 or so viral *onc* genes all have normal cellular counterparts. Apparently during the course of cell infections, the viruses picked up sequences of cellular genes that are generally thought to participate in normal growth control and differentiation. When the genes are transmitted by the viruses, however, they are expressed inappropriately, perhaps because they have been altered in some way to produce an abnormal product, or because the products are made in excessive amounts or at the wrong time. In any event, the result is malignant transformation of the affected cell.

Until the current reports, the specific effects on cell growth and differentiation of none of the viral *onc* genes and their cellular counterparts had been known. This is true even for the *src* gene, the *onc* gene of Rous sarcoma virus, although it was discovered some time ago that the product of this gene is an enzyme that attaches phosphate groups to the amino acid tyrosine in a number of proteins. But the match between the sequences of the *sis* gene product and the PDGF polypeptides leaves little doubt that the viral gene is derived either from a gene coding for PDGF or a closely related one.

PDGF stimulates the division of cells of connective tissue origin, including fibroblasts, smooth muscle cells, and glial cells. Aaronson and his colleagues have looked for expression of the *sis* gene in lines of cultured cells derived from human cancers of connective tissue cells. They find the gene product in 50 percent or more of these cell lines but not in lines derived from tumors of epithelial cells. "This raises the possibility," Aaronson says, "that the turning on of this gene in cells responsive to its action may be a step toward malignancy."

—JEAN L. MARX