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Oncogenes

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A barrage of information is now emerging about one of the thorniest and most significant problems in biology: the nature of the genetic events that trigger neoplasia. While the notion that cancer reflects somatic mutations is several decades old, only in the last few years could the relevant 'oncogenes' be identified and put to molecular dissection. The concept of oncogenes first solidified when the ability of tumourigenic viruses to induce experimental tumours in animals proved to reside in only one or two viral genes. Over the last five years, increasing evidence has accumulated that spontaneous tumours, including those of man, also reflect the action of only a few genes but, remarkably, these constitute part of the normal genome: the 'cellular oncogenes' [see Land *et al.* (1983) for a short review and Bishop (1983) for a longer one]. A cellular oncogene represents, in current dogma, a gene that can promote neoplasia if expressed inappropriately; that is, at the wrong level, in the wrong cell lineage, at the wrong stage of differentiation, or in altered form. Thus somatic mutations, or more rarely germline alterations, that change the regulation or structure of an oncogene may be conducive to the cancerous state, presumably because the gene product alters the normal growth control of the cell. The number of genes with oncogenic potential is not known, but 30–100 would be a plausible estimate.

The concept of cellular oncogenes has arisen largely from studies of retroviruses of birds and rodents. A retrovirus can exist in two states: as a single-stranded RNA molecule in viral particles and, integrated in the host genome, as a duplex DNA copy (provirus), the transcription of which regenerates both the RNA version and subgenomic RNA molecules that serve as mRNAs for the viral proteins. The tumourigenic retroviruses fall into two classes: the acutely transforming viruses, which induce tumours within a few weeks, and the chronically transforming viruses, which require months. The oncogenicity of the acute viruses resides largely in a segment of the cellular genome that each has captured. Thus a cellular gene, when expressed at elevated levels under viral control and/or with mutations acquired during viral passage, can induce tumours. To date, about 24 oncogenes have been defined by acute retroviruses and each is given an acronym related to the retrovirus in which it was first identified, e.g. *myb* from myeloblastosis virus, *myc* from myelocytomatosis, *ras* from rat sarcoma, etc. The mode of action of the chronic retroviruses is less well understood, but a significant finding was that, in most tumours induced by one such avian virus, the virus has integrated near a cellular oncogene (*myc*) and induced its expression (Hayward *et al.* 1981). Since retroviral integration is thought to occur randomly in the host genome, the slow action of these retroviruses probably reflects the millions of integration events required before expression of an effective oncogene is induced.

Certain cellular oncogenes can now be assayed directly in DNA of tumours, derived from man or animals. This remarkable advance, reviewed by Weinberg (1982), relies on the ability

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of certain recipient cell lines, most notably the mouse fibroblast line NIH3T3, to respond to certain transfected oncogenes: if the gene becomes integrated, it interferes with growth control so that the fibroblasts pile up in a focus rather than growing as a monolayer. Briefly, transfection is carried out simply by adding a calcium phosphate precipitate of tumour DNA to the fibroblast monolayer. (The calcium phosphate may facilitate uptake of DNA and protect it from nucleases while it passes to the nucleus.) Large fragments of the tumour DNA become ligated end-to-end and integrated into the genome of the recipient fibroblast. About 20–30% of tumours contain an oncogene that is active in this assay. The recipient cell line is critical because it must have a high ability to integrate exogenous DNA — an extremely variable property among cultured cells — and it must already have some of the features of a transformed cell (see below). Because only a small fraction of the tumour cell genome (perhaps 1%) is incorporated within the recipient genome, the transfection represents, in a sense, an enrichment for the active oncogene. If the donor DNA is of human origin, several cycles of transfection will leave only a few human genes in the final mouse recipient lines. By approaches such as this, active oncogenes have now been cloned from a number of human tumours (Weinberg 1982).

Significantly, most of the genes cloned using the fibroblast assay have proven to be members of the *ras* family, two of which had previously been identified in rodent acute retroviruses. It is satisfying to see two entirely independent approaches leading to the same genes. Remarkably, a single amino acid change was responsible for the conversion of one human *ras* gene into a tumourigenic form (Tabin *et al.* 1982).

The normal cellular role of most oncogenes is not known but it seems likely that many are concerned with control of cell proliferation. This notion has been strongly buttressed by the identification of the *sis* (simian sarcoma) gene product as the specific regulator platelet-derived growth factor (Doolittle *et al.* 1983) and of *erb* B (erythroblastosis) as the gene encoding the *receptor* for epidermal growth factor (Downward *et al.* 1984). The largest class of oncogenes are those exhibiting tyrosine kinase activity (i.e. the ability to phosphorylate tyrosine residues in proteins), or structural homology to tyrosine kinases. Since several specific growth factor receptors are tyrosine kinases, the tumourigenic action of these oncogenes may be to deliver an unwarranted mitogenic signal to the cell. Most likely other oncogenes have a very different role. For instance, the *myc* and *myb* products are found largely in the nucleus and may therefore have effects on transcription of other genes, or on DNA replication. Since the transmission of a mitogenic signal from a receptor at the cell surface to the DNA synthetic apparatus is likely to involve a number of intermediates, it would not be surprising if certain oncogenes proved to be associated with each of these steps. Indeed it is likely that most tumours involve interaction of the products of more than one activated oncogene, since the conversion of primary firbroblasts to a tumour can be induced by the addition of a *myc* type oncogene together with a *ras* type but not by either separately (Land *et al.* 1983). The need for cooperativity of two or more active oncogenes helps to explain the well-known increased incidence of many types of cancer with age, which bespeaks a 'multi-hit' phenomenon.

While point mutation is one way of creating a functional oncogene, more drastic DNA rearrangements, visible cytogenetically, are found in most spontaneous tumours. Indeed, as chromosome-banding techniques have increased in resolution, more and more types of neoplasia have proven to have associated karyotypic abnormalities (reviewed by Yunis 1983). These include amplified regions within chromosomes (or as 'double-minute chromosomes'), extra copies of chromosomes, deletions, and translocations. One prominent translocation found in lymphomas of man and the mouse has been extensively characterized during the last two years in several laboratories (reviewed by Klein 1983 and Perry 1983). The translocation activates the *myc* gene by putting it in the context of an immunoglobulin gene locus, a locus which is transcriptionally active in these cells. Thus, a karyotypic accident has led to the constitutive expression of an oncogene that is normally silent in mature

lymphocytes, and presumably thereby triggered the neoplastic process. It is tempting to think that many other karyotypic changes found in tumours will also represent activation of specific oncogenes.

In summary, a substantial fraction of the oncogenes have now been identified and a few associated with specific cancers. Their normal function is linked to growth control and, for two oncogenes (*sis* and *erb*B), is intimately tied to the normal growth factor–receptor pathway. The somatic mutations that subvert this normal function range from point mutations in the oncogene product (*ras*) to chromosome translocations that perturb the regulation of the oncogene (*myc*). Present efforts in this rapidly progressing field are directed towards clarifying the relation of oncogene action to growth control, in delineating how oncogenes are normally regulated and in learning how oncogenes interact to create the neoplastic state.

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