Cancer biology

Oncogenes and cell growth

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IF THE arrival of two journals* devoted to the subject marks the coming of age of oncogene research, a recent meeting† illustrated how age has a way of clouding the simple notions of youth. But, as so often in biology, new notions can flow out of unsolved problems.

Perhaps the most interesting new theme of the meeting was that normal cells, or their products, can exert control over those of their number that have been transformed into cancer cells. The control mechanisms are part of a complicated network of positive and negative controls on cell proliferation that is in continual operation. Presumably, the network is usually able to hold in check any cell in which an oncogene has arisen. But occasionally circumstances arise in which a cell escapes the net to proliferate in the uncontrolled fashion that produces a tumour.

It will take much effort to unravel the network, and particularly the inhibitors of cell proliferation, but several intriguing results and systems were described at the meeting. For example, if the viral *myc* oncogene is introduced into quail myoblast cells, they continue to proliferate rather than undergo differentiation to myotubes, the next stage in muscle formation. But differentiation is restored by the co-cultivation of the myoblasts with mammalian fibroblasts or normal quail myoblasts (F. Tato, University of Rome). In a poster, the same group extended the phenomenon to the suppression of the formation of 'foci' of *myc*-containing mouse fibroblasts (NIH 3T3 cells) when they were co-cultivated with mouse fibroblasts of a different line (C3H10T1/2).

A similar phenomenon was reported for keratinocytes provided with the viral *ras* oncogene (G.P. Dotto, Yale University). Grafted onto mouse skin, these cells result in the rapid development of carcinomas. But if the keratinocytes are mixed with fibroblasts from normal skin dermis the development of carcinomas is inhibited. Again, if the keratinocytes are injected into nude mice (whose immune system is impaired) tumours develop, whereas no tumours appear if the injected keratinocytes are first mixed with dermal fibroblasts. Thus, *ras* activation in a skin cell may not on its own be sufficient to initiate a carcinoma largely because of the inhibitory influences of adjacent cells.

By what mechanism are these 'influences' mediated? Tato reported that it is necessary for the normal cells to be continually present in his system for their inhibitory effects to be felt; the medium in which they had been growing cannot mimic them. Consequently he argues that contact between the two cell types is necessary for inhibition. But secreted peptides can also inhibit the proliferation of some cells, and a failure of such cells to respond to the inhibitory peptides, which include interferons, may be a step in the direction of tumorogenesis (A. Kimchi, Weizmann Institute, Rehovot). In her latest experiments, Kimchi finds that the addition of an interferon antibody to the medium in which rat kidney cells containing the *ras* oncogene are growing results in transformation of the cells, much as if a cooperating oncogene had been placed inside the cell. This experiment further provokes the notion that autocrine inhibition is an important mechanism in the normal control of cell growth and that disruption of the mechanism, by loss of either sensitivity to the secreted peptide or the ability to secrete it, can be a factor in tumour development.

Another factor can be the action of tumour promoters, chemicals that can push an initiated cell along the path to tumorogenicity. Phorbol esters are the favourite for study and the new focus of attention is on the gene transcription factors that mediate the induction of certain genes by TPA (12-*O*-tetradecanoyl phorbol-13-acetate) (B. Wasylyk, CNRS Strasbourg; P. Herrlich, Kernforschungs-

* *Oncogene* (Macmillan, London); *Oncogene Research* (Harwood Academic, New York).

† *Oncogenes and Growth Control* European Molecular Biology Laboratory, Heidelberg, 26 – 30 April 1987.

240-K superconductivity affirmed

FOR the past two months, rumours have been circulating about a phase in the Y–Ba–Cu–O system that superconducts at temperatures of ≥200 K. Several groups have seen drops in resistance at such temperatures, but the behaviour has not been reproducible, and many doubted that true superconductivity was being observed — a view reflected by the fact that the observations were reported mainly in newspaper articles rather than preprints. This week, superconductivity at ≥200 K finally attains scientific respectability, with the publication in *Physical Review Letters* of a paper by J.T. Chen *et al.*[1], reporting both resistance drops and the reverse a.c. Josephson effect in mixed-phase Y–Ba–Cu–O samples at temperatures near 240 K.

The phase responsible for superconductivity at ~90 K in the yttrium-based ceramics has the composition $YBa_2Cu_3O_{7-x}$ (see, for example, ref. 2). Samples far from this composition contain more than one phase, and electron microscopy reveals a granular texture with a grain size of a few micrometres. It is only in these mixed-phase samples that resistance drops near 200 K have been observed: Chen *et al.* report a decrease of ~40 per cent between 240 and 200 K, followed by a flattening and then a sudden drop starting at 90 K to zero resistance at 60 K. As Chen *et al.* say, resistance measurements alone cannot confirm that the drop at 240–200 K is caused by superconductivity, because unless there is enough of the proposed 240-K superconducting phase to form a connected path, the sample cannot exhibit zero resistance.

Chen *et al.* took advantage of the granular nature of the sample, by looking for the a.c. Josephson effect. If there is a 240-K phase, then at temperatures between 240 and 90 K the sample may be thought of as comprising numerous coupled Josephson junctions — sandwiches of insulating oxide (90-K phase) between two layers of superconductor (240-K phase). If the insulating layer is thin enough, a phase difference between the electron-pair wavefunctions on the two sides of the junction causes electron pairs to tunnel through the insulator, giving rise to a supercurrent. When there is a voltage across the junction, the phase difference increases with time, so that the current oscillates back and forth across the insulator; this is the a.c. Josephson effect. What Chen *et al.* observed was the *reverse* a.c. Josephson effect; that is, they used an alternating current to induce a constant voltage. They argue that this voltage can be distinguished from the time-averaged finite voltage that would result from rectification by diodes at grain boundaries by the observation (easily made on an oscilloscope) of a component that is constant with time. The induced d.c. voltage is observed starting at 240 K, coincident with the start of the resistance drop.

Why are the resistance measurements so irreproducible? Chen thinks the repeated cycling between room and liquid-nitrogen temperatures causes differential expansion and contraction of the grains, disrupting the electrical connections between them. Or, with time, oxygen may diffuse along grain boundaries, destroying the stoichiometry of the 240-K superconductor. The next step will be to identify and isolate the 240-K phase — only then will we know whether it is inherently unstable. Some purification will also be necessary if the four criteria of Tanaka — elucidation of the structure, observation of the Meissner effect, observation of zero resistance and experimental reproducibility[3] — are to be satisfied. Laura Garwin

1. Chen, J.T., Wenger, L.E., McEwan, C.J. & Logothetis, E.M. *Phys. Rev. Lett.* (in the press).
2. Rao, C.N.R., Ganguly, P., Raychaudhuri, A.K., Mohan Ram, R.A. & Sreedhar, K. *Nature 326*, 856-857 (1987).
3. Miura, N. *Nature* **326**, 638-639 (1987).