New gene provokes questions

A group at Imperial College, London, has characterized a set of genes which promise to be important for the understanding of normal development and the process that leads to cancer.

THE article on page 756 from Dr P. W. J. Rigby's group at Imperial College is an intriguing document which is plainly of the utmost importance, but for reasons which, at this stage, are not fully apparent. The obvious difficulty is that the observations described bear on such a variety of important but unanswered questions. What Rigby and his associates describe, in this and two closely related articles (Scott *et al. Cell* **34**, 557; 1983 and Murphy *et al. Cell*, in press), is the characterization of sets of genes, silent in most normal mouse cells but active in cells that have been transformed, or given the properties of malignancy, by the cancer-causing DNA virus SV40. So is the activity of the genes concerned characteristic of the cancerous condition? That is an obvious and important question, and for at least one set the answer must be affirmative, since the same or similar genes have been found to be activated in malignant cell lines originally derived from a variety of mouse cell types and transformed by various carcinogens, chemicals as well as viruses. This is by no means the first time a possible genetic marker has been identified in tumour cells. But what makes this discovery particularly important is that — taken with other evidence on the activation of the same genes in normal embryos — it suggests for the first time how the normal mechanism of cell differentiation may be disrupted in tumour cells.

If this were the only importance of the new development, nobody would complain. The excitement of the new development is its ramifications into other quite unexpected fields. One is the recognition that the prototype of one set of genes appears to be virtually identical to genes encoding the histocompatibility or transplantation antigens. The most familiar histocompatibility genes are those responsible for the idiosyncratic membrane proteins known as the transplantation antigens (H-2 in mice and HL-A in people), which enable the immune system to tell the difference between self and non-self. The newly characterized gene belongs to a distinct subset of these genes, closely linked to those encoding the more familiar histocompatibility genes, at what is called the *Qa/Tla* locus.

The importance of this development for the understanding of the immune system, while far from clear, seems certain to be considerable. Elizabeth Simpson gives a brief account of what this may be on page 738. Echoing Brickell *et al.*, she suggests that the genes in question may normally be active only in the earliest stages of the development of an embryo, before the maturation of the immune system, so that their products would not be recognized as "self" proteins if they should appear at some later stage. It is fascinating that this should tie in with Medawar's observation more than a decade ago that animals can be partially protected against later exposure to carcinogens by immunization with embryonic tissues.

This is not the end of the tale. The phenomena now described from Rigby's laboratory seem to be linked with the broad general question of the mechanism whereby the cells of different tissues acquire their particular properties. It has long been suspected that the apparently functionless repetitive sequences of nucleotides that are widely distributed in the chromosomes may in fact play a part in coordinating the differential activity of genes in different tissues. It is therefore notable that one of the sets of genes activated in tumour cells has now been found to share a repetitive sequence with a number of genes actively transcribed in the tissues of mouse embryos at a specific stage of development (Murphy, D. *et al.*, *Cell* December 1983, in press). This may provide for the first time a direct way of attacking the puzzling problem of differentiation.

The techniques used to isolate these sets of activated genes are of some interest in their own right. The problem faced by Rigby and his colleagues was that of detecting the activity of genes that, even in the tumour cells, were active only at relatively low levels. Their solution to this problem is, in principle, simple. In effect, they subtracted copies of all of the genes active in the normal parent cell lines from copies of the genes active in the transformed (cancerous) cell lines. What they were left with were discrete sets of genes active only in the tumour cells.

These are the techniques also being used to good effect to identify, for example, the genes responsible for antigen recognition in T lymphocytes. The problem in both cases is, so to speak, to find a needle in a haystack. The task facing Rigby's group is complicated by the huge number of needles there seems to be. There is a formidable programme of work lying ahead.

Where will it lead? For the past few years, the most immediate task in molecular biology has been to understand the regulation of genes in organisms more complicated than bacteria. It is generally assumed that this depends on the binding of regulatory proteins to specific DNA sequences flanking the functional part of genes. One suggestion for how oncogenes disrupt normal cellular behaviour is that they mimic such regulatory proteins. In the light of Rigby's results, it now seems possible that one of the products of the SV40 virus (the large T antigen) may be just such a mimic and that it may have cellular homologues normally active only at specific stages of development. A candidate for one of these homologues is the cellular *myc* gene, whose activation in lymphoid tumours is discussed by Miranda Robertson on page 733. Both the large T antigen and the *myc* product, as well as the product of a second viral oncogene (the E1A gene of adenovirus) are known, as she discusses, to be functionally equivalent in that they can confer on cells in culture the ability to proliferate indefinitely. Furthermore, there is evidence suggesting that the products of *myc* and E1A are DNA-binding proteins that are capable of activating genes that would normally be silent. Precisely what DNA sequences are bound by the E1A and *myc* products is not known, but in the case of the SV40 T antigen, the binding sites on the viral DNA have been very well characterized. And perhaps the most exciting of Rigby's recent discoveries is preliminary evidence that those binding sites have sequences in common with the repetitive element distinguishing one of the sets of genes activated in transformed cells.

This evidence that repetitive sequences — in this case relatively short ones — may be important in the coordinate regulation of groups of genes during development seems to vindicate a notion promulgated over some years by Roy Britten and Eric Davidson (see *Nature* **301**, 468; 1983). Their thesis has been precisely that small repetitive elements flanking functional genes may participate in the coordinate regulation of groups of genes during embryonic development. As an extension of that idea, they have pointed out that these small repetitive elements seem to be capable of changing their positions in the chromosomes during evolution; this, Britten and Davidson have suggested, may bring about the sort of changes in developmental regulation that have led to the evolution of new structures from old ones. □

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