Putting on the brakes

Tumour suppression

Viewing cancer as a disease of cell differentiation rather than multiplication allows a redefinition of the role of oncogenes and tumour-suppressor genes.

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It is a common assumption that somatic cells do not multiply unless they are stimulated to do so, and if they do not receive the necessary external or internal stimuli they are said to remain in the 'resting' phase. But this assumption is far from self-evident. It is entirely plausible to regard exponential multiplication, and not repose, as the cell's natural steady state. As a result of evolution, the cellular machinery for the conversion of nutrients into energy is geared towards cell multiplication. If this was not the case, it is difficult to see how natural selection, as it is currently envisaged, could operate. If, given an adequate nutrient supply and a clement physical environment, a population of cells does not multiply, those cells are not 'resting', they are repressed. The question then is not what induces cells to multiply, but what restrains them from doing so. Leaving aside conceptually unproblematic factors such as external toxicity, there appears to be only one process that represses cell multiplication under physiological conditions, and that is differentiation. Differentiation determines tissue specificity, and in doing so, it may suppress multiplication altogether, as it largely does in the central nervous system. Alternatively, it may permit multiplication to continue, but under severely restricted and regulated conditions, as in the intestine or the bone marrow. In the extreme case, it can even encompass the elimination of the cell nucleus or programmed cell death.

What, then, do we mean by oncogenes and tumour-suppressor genes? We surely do not mean that evolution generated specific genes to induce or suppress the growth of tumours. In the case of tumour-suppressor genes the position is clear. The multiplication of tumour cells is suppressed by the same set of genes as those that suppress the multiplication of normal cells of the same type during the process of differentiation; tumours arise when these genes are impaired. In *Drosophila* the experimental evidence is conclusive. Tumorous growths in the developing larva are produced at specific sites and at specific times by the impairment of genes that have critical roles in the process of normal larval differentiation. So far, such precision has not been possible with mammalian cells, but the observations that have been made are entirely consistent with this conclusion. In hybrids formed by fusing a range of different malignant tumour cells with normal diploid fibroblasts, tumorigenicity is systematically suppressed when the composite cell retains the ability to execute the differentiation programme of the fibroblast. But when the ability to execute this programme is lost, tumorigenicity reappears.

A great deal of information has been accumulated about the *retinoblastoma* (*Rb*) gene (the first mammalian tumour-suppressor gene to be isolated), the protein that it encodes and the biochemical interactions in which this protein takes part. But why, when the *Rb* gene is eliminated, is a tumour of the retina by far the commonest malignancy formed? Elimination of the *Rb* gene does indeed increase the incidence of tumours at other sites, but at a level incomparably lower than the incidence of tumours of the retina. This finding indicates that the *Rb* gene is involved in some way in the mechanisms that determine tissue specificity, but the nature of this involvement awaits a thorough molecular analysis of differentiation in the mammalian retina. The same is true for tumours at other sites. Molecular biology has provided many interesting, but partial, insights into the modes of action of tumour-suppressor genes, but in no case that I am aware of has the causal nexus between differentiation and the restraint of cell multiplication been satisfactorily elucidated in molecular terms.

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Cancer: is unrestricted cell multiplication due to a defect in differentiation?

And what about oncogenes? It was originally assumed that 'resting' cells require stimulation in order to multiply, and that cells in which multiplication is under strict physiological control require further stimulation if their multiplication is to be unbridled. That now seems very unlikely. If what has been said about the control of cell multiplication is true, then there is, in principle, only one way that oncogenes can influence cell multiplication under physiological conditions, and that is by impeding the operation of those genes that restrain this multiplication during the course of differentiation — the tumour-suppressor genes. Oncogenic mutations (and oncogenic viruses) release the brakes that tumour-suppressor genes apply.

It is often said that the growth of tumours is determined by the balance between the activity of oncogenes and that of tumour-suppressor genes. But the nature of this 'balance' is not at all clear. Is it really being proposed that the cell in some way titrates the cumulative effect of one set of genes against the cumulative effect of another? We know that a single tumour-suppressor gene may be involved, with varying degrees of efficacy, in the suppression of tumorigenesis in several different tissues. But we do not know how many genes are required to effect this suppression in any one case. It is possible that during the process of differentiation, many genes may be required acting combinatorially or sequentially or both. In the apparently simple notion of 'balance' there is thus ample room for complexity. But however complex the ultimate phenotype of a malignant cell might be, it would reduce confusion if it could be agreed that cancer, in the first instance, is not a disease of cell multiplication, but a disease of differentiation. ■

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FURTHER READING

Cavenee, W., Hastie, N. & Stanbridge, E. (eds) *Recessive Oncogenes and Tumour Suppression* (Cold Spring Harbor Lab. Press, New York, 1989).
Harris, H. *The Cells of the Body* 211–247 (Cold Spring Harbor Lab. Press, New York,1995).
Mechler, B. M. in *The Legacy of Cell Fusion* (ed. Gordon, S.) 183–198 (Oxford Univ. Press, Oxford,1994).
Harris, H. *J. Cell Sci.* **79**, 83–94 (1985).
Harris, H. *DNA Cell Biol.* **22**, 225–226 (2003).