Oncogenes homologous to steroid receptors?

SIR — Why do tumours that initially respond to hormone therapy lose their hormone responsiveness after a time and then grow autonomously? This problem is of great clinical importance, for instance in breast cancer where tumours that diminish in size after endocrine treatment almost invariably recur and then tend to progressively become nonresponsive. The discovery that many breast cancers consist of subclones of oestrogen receptor (ER)-positive and ER-negative cells[1,2] suggests that tumour progression is the survival of the 'fittest' and most malignant ER-negative subtype. But where do the hormone-independent cells come from in the first place? Are they always present or are they derived from hormone-dependent cells? And how do these manage to survive and proliferate if they do not have the oestrogen receptor to give the proliferation signal?

A general opinion is that the cells become hormone-independent because they have *lost* the receptor. But such cells should be unable to respond to their growth stimulus and so be eliminated from the tumour population. A more plausible alternative is that they have undergone a change that leads to their getting a growth signal even in the absence of ER. Steroid receptors interact with nuclear DNA at enhancer regions that regulate the transcriptional activity of structural genes[3-6]. Perhaps a mutation in the enhancer leads to its activation of genes without the need for receptor to bind to it. However, it is unlikely that the loss of ER and a mutation in the enhancer region would occur simultaneously. We suggest another explanation, namely the appearance of aberrant receptor-like molecules that bind to DNA and give a proliferation signal even in the absence of oestrogen. Unlike traditional ligand-binding studies, the recently developed monoclonal antibodies to steroid receptors have made it possible to seek aberrant receptors which fail to bind steroids in hormone-independent cells. Thus immunoreactive glucocorticoid receptors have been detected in receptor deficient (r^-), nuclear-transfer deficient (nt^-) and nuclear-transfer increased (nt^i) mouse lymphoma variant cells[7], and this has been confirmed by the finding that mRNA encoded by the receptor gene in these variants is changed quantitatively and qualitatively[8]. In r^- cells, one allele is altered so that no product is detectable with either steroid or antibody, while the other allele produces an immunoreactive polypeptide devoid of hormone-binding activity[7]. In nt^- and nt^i lymphoma cell variants, the glucocorticoid receptors react abnormally with DNA[9,10].

What are the structural changes associated with this abnormal functioning of receptors? In nt^i cells part of the receptor domain is missing which binds neither steroid nor DNA, but which may modulate nuclear association and DNA binding[7,11]. The complexes of this aberrant receptor plus glucocorticoid might still bind to the biologically relevant sites on DNA, but without this leading to transcriptional regulation[7]. Thus, the available evidence suggests that the loss of steroid responsiveness of some tumour cells may be due to alterations in the steroid receptor gene(s) leading to altered receptor molecules which may act in a 'deregulated' manner and induce cellular proliferation even in the absence of hormone. The mutated (possibly truncated) receptors may or may not retain the hormone binding properties. A biological precedent for this possibility has been described: the v-*erb-B* oncogene product is homologous to the non-hormone-binding domain of the epidermal growth factor (EGF) receptor and cells expressing the gene do not require EGF for continued growth[12]. This raises the question: are there oncogenes that are homologous to parts of the steroid receptor genes and confer loss of hormone dependence upon cells that contain them? If so, is this because the aberrant receptors produced by these oncogenes have the ability to bind to DNA without the aid of steroid hormones, and so give a continuous growth signal to the cell? In this area of research progress is rapid, so we should soon know the answer to these important questions.

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The infectious nature of prions

SIR — In a recent discussion of prions, Colin Masters emphasized that a protein-only composition of prions requires protein-directed protein synthesis for its replication, "a situation which could be without precedent in biological science"[1]. While protein-directed protein synthesis may be without precedent, protein-directed protein-folding has a precedent and could explain the infectious nature of prions.

Geneticists are well aware of this as a mechanism of gene effect in a number of dominantly inherited diseases. For instance, it is possible for an abnormal collagen to cause a severe phenotypic abnormality[2], while a non-expressing mutant for collagen is recessive[3].

This is most easily interpreted if the mutant collagen gene directs the synthesis of abnormal collagen chains which affect structure in a negative way through mixed trimers with the normal collagen chain which are conformationally abnormal. One can also see the effects of the conformation of one protein chain on another in haemoglobins (for instance, the increased affinity of a normal alpha-chain for oxygen secondary to a mutant beta-chain such as occurs with haemoglobin Ypsilanti[4]).

These protein interaction examples involve inherited genes, but the interaction is not transmitted, that is the original information is in the genome but the negative effects of an altered protein conformation are limited to the zygote. However, it is possible for such altered conformational information to be transmitted from generation to generation. The best example I know of this is that of reversed cortical pattern in *Paramecium*. Beisson and Sonneborn showed some years ago that a reversed patch of cortex could be transmitted to descendant *Paramecium* through its usual binary fission[5]. Thus, the cortex grows by the addition of macromolecules to a pre-existing cortex, receiving positional information from the pre-existing cortex. When the positional information is altered in some way, in this case by microsurgery, the abnormal information can be transmitted.

It is conceivable that the prion could be a normal protein in an abnormal configuration which, upon transmission to a new host, leads the normally synthesized protein to start folding in the new abnormal configuration, thus multiplying the number of prions in the abnormal conformation. In order to account for the increase in the number of prions, one must assume that the prion is not permanently affixed to the aggregate of 'new' and 'old' prions and that the new configuration of this normally-present protein is highly stable. Of course, such a hypothesis does not help us understand how prions cross cell membranes and the other aspects of infectivity which must be taken into account to explain their transmission between individuals.

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