Course Papers

Molecular Biology for Clinical Oncologists

A postgraduate teaching course organised by John Yarnold and Simon Powell

Academic Radiotherapy Unit, Royal Marsden Hospital, in association with the Institute of Cancer Research, London, U.K., 26–29 June 1991

The Academic Unit of Radiotherapy at the Royal Marsden Hospital in association with the Institute of Cancer Research organised a 4 day postgraduate teaching course entitled 'Molecular Biology for Clinical Oncologists' in London, 26–29 June 1991. The course concentrated on explaining recent advances in cancer research achieved through the applications of molecular techniques, particularly as they relate to the pathogenesis of human cancer and therapeutic responses to radiation and drugs. No prior knowledge of the field was assumed. Invited speakers were clinical scientists or scientists directly involved in laboratory programmes related to the topics they presented. The following articles are based on the course book that was provided.

The first two days explained how cancer genes are recognised and how they disrupt cell behaviour. Specific examples were chosen to illustrate multistage carcinogenesis in adult and paediatric cancers. The principles and applications of the polymerase chain reaction (PCR) to applied research were also discussed. The third day included presentations on the future of gene therapy. The last day focussed on how radiation and drugs induce damage in DNA, how damage is modified by repair mechanisms, and how residual DNA damage determines cell fate. A second teaching course on Molecular Biology for Clinical Oncologists is planned for 1–3 July, 1992. Further information can be obtained from J. R. Yarnold at the Royal Marsden Hospital.

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Understanding DNA Damage and Repair: How Useful will it be Clinically?

Anna M. Cassoni

UNDERSTANDING OF DNA damage and repair is potentially useful clinically in two major ways; the prediction of response in the individual patient and the modification of response to cytotoxic therapy. We are currently unable to predict reliably which patients will respond to therapy. Tumour resistance remains a problem for both local and systemic therapies. Approaches to overcoming this include the development of new drugs within recognised groups with different binding specificities and the modification of repair by enzyme inhibition. The more effective use of radiation alone or in combination may be helped by the appreciation that certain types of damage are less repairable than others (as in high linear energy transfer radiations by external beam or incorporated radioisotopes), or how molecules such as thiols modify damage. Predictive assays of sensitivity to both radiation and cytotoxic therapy are currently being assessed based primarily on biological measures such as cell proliferation. Should these prove useful, direct measures of DNA damage may provide the same information more rapidly and reliably. The transition from the laboratory, to clinical practice, however, presents several problems particularly in the testing of new treatment strategies based on damage modification. The current philosophy of testing is based on randomised trials; large groups of patients in broad prognostic categories such that the small improvements currently considered realistic can be detected. It seems unlikely that any one of the modifications we have been considering will produce sufficiently large improvements across even a single tumour category to be detected in this way. Realistic goals for studies, therefore, must be identified, with appropriate patient selection for each

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modality. In order to demonstrate an improvement in these subgroups multicentre studies will be required. The improvement in survival produced by even small percentage increments are worthwhile. For example, a 15% improvement in local control rates for carcinoma of the cervix and bladder only could result in increased survival of over 1500 patients annually. The change, however, from an approach based on broad prognostic categories with one therapeutic manoeuvre to that based on multiple subgroups selected for different therapeutic modalities is a considerable change from current practice.

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How are Cancer Associated Genes Activated or Inactivated?

Leanne M. Wiedemann and Gareth J. Morgan

Altered behaviour or the transformation of a cell can result from the abnormal expression of some oncogene products. Elevated or inappropriate expression can result from (i) mutations in the regulatory region of the gene, (ii) aberrant expression of a transcription factor involved in the regulation of the gene, (iii) gene amplification, or (iv) the insertion of a viral promoter upstream of the gene. In addition, an alteration in the product of a proto-oncogene can lead to the acquisition of a transforming activity. Such changes have been shown to include (i) point mutation, (ii) deletion, and (iii) the formation of fusion genes. Finally, the loss of activity of a gene product can contribute to transformation. This can come about by (i) small or large deletions, (ii) point mutations which abolish function or expression of an intact protein, or (iii) mutations which lead to a protein with an activity which can inhibit the suppressor activity of the normal allele.
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INTRODUCTION

MECHANISMS LEADING to the activation or inactivation of genes found to contribute to the formation of a tumour are many and varied. These mechanisms are not necessarily mutually exclusive and several may be involved in the activation or inactivation of a gene product. It is also important to remember that the activation (or inactivation) of a single copy of an individual gene along a signalling pathway is not sufficient to result in a fully malignant change in the behaviour of the cell. In most forms of cancer only one or two of the five or more oncogenic steps have been pin-pointed [1].

This short review is not a complete list of changes known to occur in cancer, but gives a few examples of those that have been characterised to date.

POINT MUTATION

RAS mutations

One of the first oncogenes to be shown to be activated by a point mutation was the human homologue of the Ha-*RAS* gene. The altered activity of the RAS proteins was first identified in a transformation assay where both the appearance and behaviour of an indicator fibroblast cell line, NIH 3T3, was altered following transfection with DNA. The DNA for these experiments originated from the EJ bladder carcinoma cell line. The transforming allele of the *RAS* gene was shown to contain a single amino acid change which had converted the cellular proto-oncogene into an oncogene. Additional activating point mutations have been identified in Ha-*RAS* and other members of the *RAS* gene family [2]. Normal RAS proteins have been shown to bind and hydrolyse GTP to GDP. Many of the mutations have been shown to affect the ability of these proteins to hydrolyse the GTP molecule; since *RAS* transmits a signal when in the GTP-bound state, these mutations result in the constitutive activation of the complex. The molecular consequences of this change are still the subject of intense investigation in a number of laboratories.

Other genes encoding GTP-binding proteins have been identified which have been implicated in tumorogenicity (guilt by association) due to the identification of point mutations in some endocrine tumours. Examples include the *GIP* gene in carcinoma of ovary and adrenal gland and the *GSP* gene in adenoma of the pituitary gland and carcinoma of the thyroid gland [3].

Other activating mutations

In addition, a number of other proto-oncogenes have been shown to acquire point mutations in certain forms of cancer [4]. Point mutations have been identified in c-*FMS* (CSF-1 receptor) in monocytic leukaemias [5] which may result in the constitutive activation of the protein tyrosine kinase activity of the receptor in the absence of the growth factor ligand. Other mutations and structural alterations which can lead to the activation of growth factor receptors are reviewed by Aaronson and Tronick [6].

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